M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: 12 November 2009

FROM: Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food & Drug Administration

TO: Members and Consultants,
Endocrinologic & Metabolic Drugs Advisory Committee

SUBJECT: 15 December 2008, Advisory Committee meeting for rosuvastatin (Crestor™)

Thank you for agreeing to participate in the December 15, 2009, advisory committee meeting. This meeting is being held to discuss the results of the JUPITER trial. This study examined the efficacy and general safety of rosuvastatin in approximately 17,000 middle-aged and older men and women with LDL-C levels < 130 mg/dl and high sensitivity C-reactive protein (hsCRP) values $\geq$ 2 mg/L.

Rosuvastatin is a member of the statin class of medications. The first statin approved in the United States was lovastatin in 1987. This was followed by the approval of pravastatin and simvastatin in 1991, fluvastatin in 1993, atorvastatin in 1996, cerivastatin in 1997, and rosuvastatin in 2003. All the statins were approved based on their ability to significantly reduce levels of LDL-C, a validated surrogate for cardiovascular disease. The results of placebo-controlled outcomes trials conducted in the 1990s and early 2000s led the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults to recommend statins as first-line therapy for the prevention of cardiovascular disease (CVD) in high-risk subjects with hypercholesterolemia.

Two years prior to the approval of rosuvastatin in 2003, a retrospective analysis of a clinical trial was published raising the hypothesis that statin therapy may reduce the risk for cardiovascular disease in subjects with "normal" levels of LDL-C but elevated levels of hsCRP, a biomarker of inflammation. Inflammation is believed to play a causal role in atherosclerosis and thrombosis.

The JUPITER trial prospectively tested the hypothesis that treatment with 20 mg once-daily rosuvastatin would reduce the risk for cardiovascular events in asymptomatic subjects with elevated levels of hsCRP not considered appropriate for statin therapy because of "normal" levels of LDL-C. It was also hypothesized that treatment with rosuvastatin would reduce the incidence of type 2 diabetes.

Designed as a three or four-year trial, JUPITER was stopped after a median follow-up of 1.9 years due to adequate statistical evidence of efficacy. The percentage of subjects who had a first major cardiovascular event defined as cardiovascular death, non-fatal stroke, non-fatal MI, hospitalization for unstable angina, or arterial revascularization was 2.8% in the placebo group compared with 1.6% in the rosuvastatin group ($p<0.001$). The incidence of physician-reported type 2 diabetes was actually higher in the rosuvastatin vs. the placebo group (2.8% vs. 2.3%), a difference of nominal statistical significance.

There were more subjects in the rosuvastatin group compared with the placebo group who died due to a gastrointestinal event and more reports of confusional state in active vs. placebo-treated subjects. Additional information about these adverse events is provided in the FDA briefing document.

Rosuvastatin is currently indicated:

- for patients with primary hyperlipidemia and mixed dyslipidemia as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C
- for patients with hypertriglyceridemia as an adjunct to diet
- for patients with homozygous familial hypercholesterolemia to reduce LDL-C, total-C, and ApoB
- for patients with primary dysbetalipoproteinemia as an adjunct to diet
- for slowing the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C as an adjunct to diet
- for pediatric patients 10 to 17 years of age with heterozygous familial hypercholesterolemia to reduce elevated total-C, LDL-C, and ApoB after failing an adequate trial of diet therapy

Based on the results of JUPITER, the sponsor Astra Zeneca is requesting that the following be added to the Indications and Usage section of rosuvastatin labeling: "For the prevention of cardiovascular disease in adult patients with an increased risk of cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated hsCRP level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to:

- reduce the risk of total mortality
- reduce the risk of cardiovascular death
- reduce the risk of stroke
- reduce the risk of myocardial infarction
- reduce the risk of arterial revascularization
- reduce the risk of unstable angina"

As you read the briefing material and listen to the presentations on December 15th, please keep in mind that an estimated 6 million middle-aged and older men and women in the United States satisfy the JUPITER hsCRP and LDL-C entry criteria. Further, we ask that you consider the following comments and question, which you will be asked to respond to at the meeting:

1. In the JUPITER clinical trial, there were 13 deaths due to Gastrointestinal Disorders in the treatment arm versus 1 in the placebo arm. Please comment on the significance of this imbalance.
2. In the JUPITER clinical trial, there were 18 patients who reported a confusional state in the treatment arm versus 4 in the placebo arm. Please comment on the significance of this imbalance.
3. In the JUPITER clinical trial, there was a statistically significant increase in investigator-reported diabetes mellitus in the treatment arm versus the placebo arm, 2.8% vs. 2.3%, respectively with a hazard ratio of 1.27 (95% CI 1.05, 1.53; p=0.015). Please comment on the significance of this imbalance.
4. Has the sponsor provided sufficient evidence of a favorable benefit-to-risk profile for rosuvastatin for the primary prevention of CVD in middle- and older-aged low-to-moderate CVD risk individuals with levels of LDL-C <130 mg/dL and hsCRP ≥2 mg/L?

Clinical Briefing Document
Endocrine and Metabolic Drugs Advisory Committee Meeting
December 15, 2009

New Drug Application 21-366/S016: CRESTOR® (rosuvastatin calcium)
Sponsor: AstraZeneca
Clinical Reviewer: Mary Dunne Roberts, MD

Introduction:

Product information

CRESTOR® (rosuvastatin calcium) is a member of the statin class of lipid-lowering compounds, which inhibits the rate-limiting enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase decreasing cholesterol synthesis. Approval in the United States occurred on 12 August 2003. Currently, rosuvastatin is available in 5, 10, 20, and 40 mg tablets and is indicated for:

1. Patients with primary hyperlipidemia (heterozygous familial and non-familial) and mixed dyslipidemia (Fredrickson Type IIa and IIb) as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C
2. Patients with hypertriglyceridemia (Fredrickson Type IV) as an adjunct to diet
3. Patients with primary dysbetalipoproteinmeia (Type III hyperlipoproteinemia) as an adjunct to diet
4. Patients with homozygous familial hypercholesterolemia to reduce LDL-C, total-C, and ApoB
5. Slowing the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C as an adjunct to diet
6. Pediatric patients 10 to 17 years of age with heterozygous familial hypercholesterolemia (HeFH) to reduce elevated total-C, LDL-C and ApoB after failing an adequate trial of diet therapy.

This NDA supplement presents data from one pivotal efficacy study Study D3560L00030 **JUPITER**: "**J**ustification for the **U**se of statins in **P**rimary prevention: an **I**ntervention **T**rial **E**valuating **R**osuvastatin": A randomized, double-blind, placebo-controlled, multicenter, Phase 3 study of rosuvastatin 20 mg in the primary prevention of cardiovascular events among subjects with low levels of LDL-cholesterol (<130 mg/dL), no overt cardiovascular disease, an older age (≥50 years for men, ≥60 years for women) and elevated levels of high-sensitivity C-reactive protein (hsCRP) (≥2.0 mg/L) to support an indication proposed by AstraZeneca for:

- Prevention of cardiovascular disease in adult patients with an increased risk of cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated hsCRP level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to:
    - reduce the risk of total mortality
    - reduce the risk of cardiovascular death
    - reduce the risk of stroke
    - reduce the risk of myocardial infarction (MI)
    - reduce the risk of arterial revascularization
    - reduce the risk of unstable angina

Background

In the United States, coronary heart disease (CHD) continues to be the leading cause of death among adults.[1] High levels of low-density lipoprotein cholesterol (LDL-C) have been identified as a major risk factor for CHD. It has also been established that the lowering of LDL-C levels conveys a significant reduction in the risk of major cardiovascular events (MCE) in persons with and without established CHD. One way to effectively guide treatment prevention to assess risk based on the ATP-III guidelines of the National Cholesterol Education Program (NCEP) which sets goals for optimal LDL-C levels based on an individual's calculated risk.[2]

The ATP-III guidelines, updated in 2004[3], categorize adults into 3 risk categories: (1) established CHD and CHD risk equivalents, (2) two or more risk factors, and (3) zero to one risk factors. In individuals with at least two of the ATP-III major risk factors defined as age (≥ 45 years in men, ≥ 55 years in women), cigarette smoking, hypertension (blood pressure ≥ 140/90 mmHg or on antihypertensive medication), low HDL-C (<40 mg/dl), and family history of premature CHD further categorization of an individual's hard coronary heart disease (myocardial infarction and coronary death) 10-year risk is recommended. Ten-year risk is calculated using a subset of the Framingham risk factors which group individuals into 10-year risk levels of <10%, 10-20%, and >20%. Persons with diabetes mellitus or multiple risk factors and 10-year risk >20% are considered as having a CHD risk equivalent.

The NCEP 2004 update reduced the LDL-C threshold for drug therapy for high risk persons (CHD/CHD risk equivalent) to 100 mg/dL with the continued LDL-C goal of <100 mg/dL or the optional goal of < 70 mg/dL for very high risk individuals - those who have had a recent heart attack, or those who have cardiovascular disease combined with either diabetes, or severe or poorly controlled risk factors (such as continued smoking), or metabolic syndrome.[4] In addition, for those defined as moderately high risk (2+ risk factors and 10-year risk of 10-20%), the LDL-C goal remained at < 130 mg/dL; however there were two modifications: a LDL-C goal of <100 mg/dL was considered a therapeutic option and for those individuals with LDL-C values of 100-129 mg/dL at baseline or on lifestyle therapy initiation of a LDL-lowering therapy to achieve a LDL-C < 100 mg/dL was proposed as a reasonable treatment option within this moderately high risk group.

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[1] Heron et al. Deaths: Final Data for 2006. National Vital Statistics Reports; Vol 57 No 14. Hyattsville, MD: National Center for Heatlh Statistics; 2009. Accessed at www.cdc.gov/nchs on October 15, 2009.
[2] National Heart Lung and Blood Institute, Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001; 285 (19): 2486-97.
[3] Grundy et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. JACC 2004; 44: 720-32.
[4] www.nhlbi.nih.gov/guidelines/cholesterol/upd-info_prof htm. Accessed online October 27, 2009.

Table 1: NCEP 2004 Update of ATP-III LDL-C goals and cutpoints for treatment

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy**
High risk: CHD* or CHD risk equivalents† (10-year risk >20%)	<100 mg/dL (optional goal: <70 mg/dL)‖	≥100 mg/dL#	≥100 mg/dL†† (<100 mg/dL: consider drug options)**
Moderately high risk: 2+ risk factors‡ (10-year risk 10% to 20%)§§	<130 mg/dL¶	≥130 mg/dL#	≥130 mg/dL (100–129 mg/dL; consider drug options)‡‡
Moderate risk: 2+ risk factors‡ (10-year risk <10%)§§	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk: 0–1 risk factor§	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)

Source: Grundy et al.

Individuals eligible for enrollment in the JUPITER trial would not have been considered for statin therapy according to the NCEP ATP-III 2001 guidelines. However, according to the NCEP 2004 update drug therapy could be considered in moderately high risk persons when LDL-C levels are 100 to 129 mg/dL at baseline to achieve a LDL-C of < 100 mg/dL.

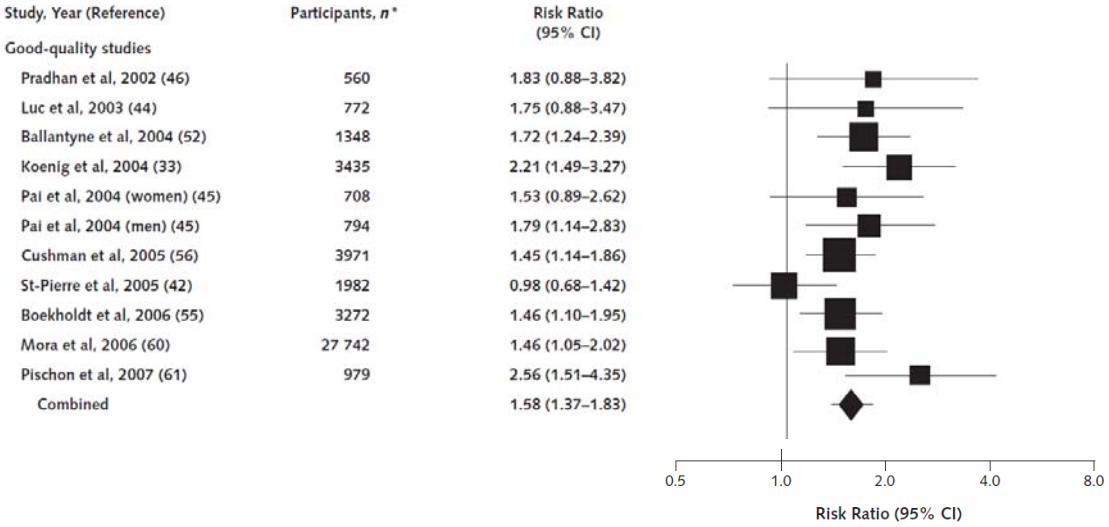
Both the ATP-III guidelines and Framingham risk scores rely on conventional risk factors (hyperlipidemia, smoking, diabetes, hypertension) and do not include other emerging non-traditional risk factors such as hsCRP. It has been suggested that over 50% of patients with CHD lack conventional risk factors.[5,6] Others contend that 80 to 90% of patients with CHD do exhibit conventional risk factors.[7,8] In a recent report, 41.5% of people hospitalized with CHD with no history of previous atherosclerotic disease, CHD, or diabetes had LDL-C levels below100 mg/dL.[9] The debate regarding these potential at-risk individuals lacking conventional risk factors has fostered research into improving identification and risk assessment by non-traditional risk factors.

High sensitivity CRP is a non-specific biomarker of inflammation. Inflammation has been implicated in contributing to the plaque instability of atherosclerotic disease.[10] Epidemiologic data have demonstrated that elevated hsCRP is associated with obesity,[11] conventional cardiovascular risk factors,[12] and increased risk of CHD.[13,14] In a recent

[5] Futterman et al. Fifty percent of patients with coronary artery disease do not have any of the conventional risk factors. Am J Crit Care 1998; 7:240-4.
[6] Hennekens et al. Increasing burden of cardiovascular disease: current knowledge and future directions for research on risk factors. Circulation 1998; 97:1095-1102.
[7] Greenland et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA 2003; 290:891-897.
[8] Khot et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA 2003; 290:898-904.
[9] Sachdeva et al. Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalizations in Get With The Guidelines. Am Heart J 2009; 157:111-7.e2.
[10] Ross et al. Atherosclerosis-an inflammatory disease. NEJM 1999; 340:115-26.
[11] Lemieux et al. Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. Arterioscler Thromb Vasc Biol. 2001;21:961-7.
[12] Miller et al. High attributable risk of elevated C-reactive protein level to conventional coronary heart disease risk factors; The Third National Health and Nutrition Examination Survey. Arch Intern Med 2005; 165:2063-8.

meta-analysis for the U.S. Preventive Services Task Force, 10 studies determined by the USPSTF to be of good quality that adjusted for all Framingham risk factors demonstrated a relative risk for CHD of 1.58 (CI, 1.37 to 1.83) for high (>3 mg/L) versus low (<1 mg/dL) hsCRP (Figure 1).[15]

Figure 1: Risk ratio for CHD associated with hsCRP level >3 versus <1 mg/L



In 2002, neither the Centers for Disease Control and Prevention nor the American Heart Association endorsed global screening for hsCRP for cardiovascular risk assessment but did recommend the "optional use of hsCRP to identify patients without known cardiovascular disease who may be at higher absolute risk than estimated by major risk factors.[16] Specifically, those patients at intermediate risk (10-year 10-20% CHD risk) in whom the physician may need additional information to guide considerations of further evaluation or therapy may benefit from measurement of hsCRP." Levels of hsCRP were assigned risk categories of low (<1 mg/L), average (1-3 mg/L), and high (>3 mg/L).

Support for the identification and treatment of individuals at higher cardiovascular risk based on hsCRP was generated from the AFCAPs/TexCAPs trial. In this randomized, placebo-controlled primary prevention trial of 6605 people with normal to mildly elevated total cholesterol and LDL-C levels and without clinically evident atherosclerotic cardiovascular disease it was noted in a post-hoc evaluation, that subjects with a below median LDL-C (149 mg/dL) but above median hsCRP (1.6 mg/L) had similar placebo-

[13] Cushman et al. C-reactive protein and the 10-year incidence of coronary heart disease in older men and women: the cardiovascular health study. Circulation 2005;112:25-31.
[14] Pischon et al. Comparison of relative and attributable risk of myocardial infarction and stroke according to C-reactive protein and low-density lipoprotein cholesterol levels. Eur J Epidemiol 2007;22:429-38.
[15] Buckley et al. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. Ann Intern med 2009;151:483-95.
[16] Pearson et al. Markers of inflammation and cardiovascular disease: application to clinical and public healthy practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499-511.

event rates of coronary events as subjects with above median LDL-C values.[17] In addition, this subgroup when treated with lovastatin demonstrated a risk reduction similar to their high LDL-C counterparts.

Based on the National Health and Nutrition Examination Survey (NHANES) data the number of United States adults who would be considered for statin therapy according to JUPITER eligibility criteria was estimated. Population estimates were based on a sample number of cases and weighted to the civilian noninstitutionalized U.S. population.[18] This calculation estimated approximately 3.9 million men age ≥ 50 years and 2.6 million women ≥ 60 years have an LDL <130 mg/dL and hsCRP ≥ 2.0 mg/L. This group was comprised of 57% whites, 15% blacks, and 26% Hispanics. In a separate estimation which included younger adults, who would have been excluded from the JUPITER trial because of age, approximately 14.5 million men and 22.2 million women ≥ 20 years have LDL <130 mg/dL and hsCRP ≥ 2.0 mg/L. In addition, the authors estimated an additional 10 million older adults have lipid levels below their NCEP/ATP-III cutpoints for therapy who would become eligible to initiate statin therapy based on an elevated hsCRP ≥ 2.0 mg/L.

Currently Available Treatment for Indications

Currently, five of the seven FDA-approved statins contain primary or secondary cardiovascular disease prevention indications in their labels. These are summarized in Table 2 along with CRESTOR's proposed indication. Further description of the patient populations of several large randomized controlled primary prevention trials are compared to the JUPITER trial in Table 3 adapted from Brugts et al.[19]

[17] Ridker et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. NEJM 2001;344:1959-65.
[18] Michos et al. Prevalence of low Low-Density Lipoprotein cholesterol with elevated high sensitivity C-reactive protein in the U.S.: Implications of the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) Study. JACC 2009;53:931-5.
[19] Brugts et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomized controlled trials. BMJ 2009;338:b2376.

Table 2: Current statin label indications for primary and secondary prevention of major cardiovascular events

Statin	CV trials in label	Patient population studied	Duration of study	Clinical endpoints used	Date of indication approval	Indication in label
CRESTOR (Rosuvastatin)	**JUPITER**	**N=17802 (6765 women) LDL < 130 mg/dL (mean 104 mg/dL) CRP ≥ 2 mg/L (median 4.3 mg/L) +1 risk factor for CHD**	**Median 1.9 years of 20 mg or placebo**	**MCE (CV death, MI, stroke, unstable angina, or arterial revasc) (RRR 44%)**	**?**	**(Proposed) Primary prevention CHD:** ***In adult patients with an increased risk of cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated hsCRP level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to:*** • ***reduce the risk of total mortality*** • ***reduce the risk of cardiovascular death*** • ***reduce the risk of stroke*** • ***reduce the risk of myocardial infarction*** • ***reduce the risk of arterial revascularization*** • ***reduce the risk of unstable angina***
PRAVACHOL (Pravastatin)	WOSCOPS (R, DB, PC)	N=6595 men 45-64 yo No previous MI LDL-C 156-254 mg/dL	Median 4.8 years of 40 mg or placebo	CHD death or nonfatal MI (RRR 31%)	2 July 1996	Primary prevention CHD: *In hypercholesterolemic patients without clinically evident coronary heart disease, PRAVACHOL is indicated to* • *Reduce the risk of MI* • *Reduce the risk of undergoing myocardial revascularization procedures* • *Reduce the risk of CV mortality with no increase in death from non-CV causes*
	CARE (DB, PC)	N=4159 (3583 men, 576 women) h/o MI in previous 3-20 months Normal (<75th%ile) total cholesterol levels LDL-C 101-180 mg/dL (mean 139 mg/dl)	Mean 4.9 years of 40 mg or placebo	CHD death or nonfatal MI (RRR 24%)	27 March 1998	Secondary prevention CHD: *In patients with clinically evident coronary artery heart disease, PRAVACHOL is indicated to* • *Reduce the risk of total mortality by reducing coronary death* • *Reduce the risk of MI* • *Reduce the risk of undergoing myocardial revascularization procedures* • *Reduce the risk of stroke and stroke/TIA*
	LIPID (R, DB, PC)	N=9014 (7498 men, 1516 women, 3514 ≥65 y, 782 DM) h/o MI or hospitalized for unstable angina in previous 3-36 months LDL-C 46-274 mg/dL (mean 150 mg/dL)	Median 5.9 years of 40 mg or placebo	CHD death (RRR 24%)	10 February 2000	

Statin	CV trials in label	Patient population studied	Duration of study	Clinical endpoints used	Date of indication approval	Indication in label
ZOCOR (Simvastatin)	4S (R, DB, MC, PC)	N=4444 (844 women) 35-71 yo	Median 5.4 years of 20-40 mg or placebo	1.Total mortality (RRR 30%) 2. CHD death, non-fatal acute MI (RRR 34%)	31 March 1998	Primary and Secondary prevention CHD: *In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, ZOCOR is indicated to* • *Reduce the risk of total mortality by reducing CHD deaths* • *Reduce the risk of non-fatal myocardial infarction and stroke* • *Reduce the need for coronary and non-coronary revascularization procedures*
	HPS (MC, DB, PC)	N=20536 (4107 women) 40-80 yo 51% LDL≤130 mg/dL Total-C ≥ 135 mg/dL Substantial 5-year risk of CV death	Mean 5 years of 40 mg or placebo	Mortality (RRR 13%) CHD death (RRR 18%)	16 April 2003	
MEVACOR (Lovastatin)	AFCAPS/TexCAPS (R, DB, PC)	N=6605 (997 women) Total-C 180-264 mg/dL LDL-C 130-190 mg/dL, HDL ≤ 45 mg/dL	Median 5.1 years of 20-40 mg or placebo	MCE (MI, unstable angina, sudden cardiac death) (RRR 37%)	11 March 1999	Primary prevention CHD: *In individuals without symptomatic cardiovascular disease, average to moderately elevated total-C and LDL-C, and below average HDL-C, MEVACOR is indicated to reduce the risk of* • *MI* • *Unstable angina* • *Coronary revascularization procedures*
LESCOL/ LESCOL XL (Fluvastatin)	LIPS (R, MC, DB, PC)	N=1677 with CHD and PCI 18-80 yo 268 women LDL-C 42-243 mg/dL (mean 132 mg/dL)	Median 3.9 years 40 mg BID or placebo	MCE (CHD death, nonfatal MI, revascularization) (RRR 22%)	27 May 2003	Secondary prevention CHD: *In patients with coronary heart disease, Lescol and Lescol XL are indicated to reduce the risk of undergoing coronary revascularization procedures*
LIPITOR (Atorvastatin)	ASCOT-LLA (R, MC, DB, PC)	N=10305 hypertensive 40-80 yo No MI ≥ 3 CV risk factors	Median 3.3 years 10 mg or placebo	CHD death or nonfatal MI (RRR 36%)	30 July 2004	Primary prevention CHD: *In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease, such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, LIPITOR is indicated to* • *Reduce the risk of MI* • *Reduce the risk of stroke* • *Reduce the risk for revascularization procedures and angina* *In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, LIPITOR is indicated to* • *Reduce the risk of MI* • *Reduce the risk of stroke*
	CARDS (R, MC, DB, PC)	N=2838 (908 women) 40-75 yo Type 2 diabetes No CVD LDL≤160 mg/dL (median LDL 120 mg/dL)	Median 3.9 years 10 mg or placebo	MCE (MI, acute CHD death, unstable angina, coronary revasc, stroke) (RRR 37%)	21 September 2005	

Statin	CV trials in label	Patient population studied	Duration of study	Clinical endpoints used	Date of indication approval	Indication in label
	TNT	N=10001 (1900 women) h/o CHD Achieved LDL-C <130 mg/dL after run-in period of 10 mg Lipitor	Median 4.9 years 80 mg vs 10 mg Lipitor	MCE (CHD death, nonfatal MI, resuscitated cardiac arrest, fatal and nonfatal stroke) (RRR 22%)	2 March 2007	Secondary prevention CHD: *In patients with clinically evident coronary heart disease, LIPITOR is indicated to* • *Reduce the risk of non-fatal MI* • *Reduce the risk of fatal and non-fatal stroke* • *Reduce the risk for revascularization procedures* • *Reduce the risk of hospitalization for CHF* • *Reduce the risk of angina*
	IDEAL (R, OL, blinded endpoint)	N=8888 (1688 women) h/o CHD Mean LDL 121.5 mg/dL	Median 4.8 years 80 mg Lipitor vs 20-40 mg simva	MCE (fatal CHD, nonfatal MI and resuscitated cardiac arrest) NS (p=0.07)	2 March 2007	

Table 3: Baseline demographics and characteristics of statin primary cardiovascular prevention trials (adapted from Brugts et al)

Characteristic	WOSCOPS 1995[20]	AFCAPS/ TexCAPS 1998[21]	PROSPER *[22] 2002	ALLHAT-LLT 2002[23]	ASCOT-LLA 2003[24]	HPS*[25] 2003	CARDS 2004[26]	ASPEN*[27] 2006	MEGA 2006[28]	JUPITER 2008[29]
Target population	Men with hypercholesterolemia and no history of MI	People with normal to mildly elevated cholesterol levels (TC 180 to 264 mg/dL; LDL 130-190 mg/dL; HDL ≤ 45 mg/dL-men) (without atherosclerotic cardiovascular disease)	Elderly people with cardiovascular risk factors	People with hypertension, moderate hypercholesterolemia, and at least one coronary heart disease risk factor	People with hypertension, average or lower cholesterol levels, and at least three other risk factors	People with diabetes	People with diabetes and low LDL (≤ 160 mg/dL) and no history of CV disease	People with diabetes and low LDL below guideline targets	People with hypercholesterolemia and no history of CHD or stroke	People without vascular disease, low LDL, and hsCRP ≥2 mg/L
Design	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized double-blind, placebo	Randomized controlled trial (control=usual care)	Randomized, double-blind, placebo-controlled	Randomized, double-blind placebo controlled	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo controlled	Randomized, double-blind, placebo controlled (control=diet)	Randomized, double-blind, placebo-controlled

[20] Shepherd et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. NEJM 1995; 333:1301-7.
[21] Downs et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. JAMA 1998; 279:1615-22.
[22] Ford et al. A prospective study of pravastatin in the elderly at risk (PROSPER): Screening experience and baseline characteristics. Curr Control Trials in cardiovasc med 2002;3:1-8.
[23] Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: ALLHAT-LLT. JAMA 2002; 288:2998-3007.
[24] Sever et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicenter randomized controlled trial. Lancet 2003; 361: 1149-58.
[25] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trial. Lancet 2003;361:2005-16.
[26] Calhoun et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): a multicenter randomized placebo-controlled trial. Lancet 2004;364:685-96.
[27] Knopp et al. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes (ASPEN). Diabetes Care 2006; 29:1478-85.
[28] Nakamura et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA study): a prospective randomized controlled trial. Lancet 2006;368:1155-63.
[29] Ridker et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. NEJM 2008;352:2195-207.

Characteristic	WOSCOPS 1995[20]	AFCAPS/ TexCAPS 1998[21]	PROSPER *[22] 2002	ALLHAT-LLT 2002[23]	ASCOT-LLA 2003[24]	HPS*[25] 2003	CARDS 2004[26]	ASPEN*[27] 2006	MEGA 2006[28]	JUPITER 2008[29]
			controlled							
No of participants (statin/control)	6595 (3302/3293)	6605 (3304/3301)	3239 (1585/1654)	10355 (5170/5185)	10305 (5168/5137	2912 (1455/1457)	2838 (1428/1410)	1905 (959/946)	7832 (3866/3966)	17802 (8901/8901
Mean follow-up (years)	4.9	5.2	3.2	4.8	5.5†	4.8	3.9†	4.0†	5.3	1.9†
Drug	Pravastatin	Lovastatin	Pravastatin	Pravastatin	Atorvastatin	Simvastatin	Atorvastatin	Atorvastatin	Pravastatin	Rosuvastatin
Dose (mg/day)	40	20-40	40	20-40	10	40	10	10	10-20	20
Mean age (range)(years)	55 (45-64)	58 (45-73)	75 (70-82)	66.4 (51-81)	63.1 (40-79)	NA (40-80)	61.5 (40-75)	60.5 (40-75)	58.3 (40-70)	66† (60-71)
Women (%)	0	15	58‡	49	18.7	NA	32	38	68.4	37.9
With diabetes (%)	1 (self-reported)	3.8	12.2‡	34.4	24.7	100	100	100	21	0
Current smoker (%)	44	13	33.4‡	23.3	33.2	NA	22	12	21	16
Hypertension (%)	16 (self-reported)	22	71.6‡	89.9	80.3	NA	79.5	52	42	57
Mean BMI (kg/m^2)	26	26.8	27‡	29.9	28.6	NA	28.7	28.0	23.8	28.4†
Mean SBP (mmHg)	136	138	156.6‡	145	164.2	NA	144	133	132	134†
Mean DBP (mmHg)	84	78	85.2‡	84	95	NA	83	77.1	78.4	80†
Framingham risk score <10% 10-20% >20%	NR	NR 40% 60% (FRS >10%)	NR	NR	 6% 31% 63%	NR	 8.31 37.32 54.37	NR	NR	 40.5 50.6 8.8
Baseline lipid levels in mg/dL (% change)										
Total cholesterol	272 (-20.0)	221 (-19.3)	220 (NA)	224 (-9.6)	212 (-18.2)	NA	207 (-21.8)	193 (-19.8)	243 (-11)	183 (-23)
LDL	192 (-26.0)	150 (-26.5)	146 (NA)	146 (-16.7)	131 (-27.6)	NA	117 (-33.9)	116 (-30.5)	154 (-18)	104 (-40)
HDL	44	36 (4.8)	50.2 (NA)	48 (0.9)	50 (1.5)	NA	54 (4.0)	46 (1.9)	58 (5.0)	49 (4.0)
Triglycerides	163	158 (-12.7)	133 (NA)	152 (<0.1)	152 (-12.6)	NA	178 (-15.9)	142(-4.7)	124 (-7)	138 (-14)
hsCRP, median (mg/L)		1.6					1.4			4.2
Primary endpoint	Nonfatal MI or CHD death	Sudden cardiac death, fatal and nonfatal MI, unstable angina	Coronary heart death, non-fatal MI	All-cause mortality	Non-fatal MI and fatal CHD	Major coronary events (non-fatal MI, CHD death), strokes, and	Acute coronary heart disease event (MI, unstable angina, CHD	CV death, non-fatal MI, non-fatal stroke, revasc, resuscitated	Fatal and non fatal MI, angina, cardiac and sudden death, coronary revasc	CV death, non-fatal MI, non-fatal stroke, unstable angina, or arterial revascularization

Characteristic	WOSCOPS 1995[20]	AFCAPS/ TexCAPS 1998[21]	PROSPER *[22] 2002	ALLHAT-LLT 2002[23]	ASCOT-LLA 2003[24]	HPS*[25] 2003	CARDS 2004[26]	ASPEN*[27] 2006	MEGA 2006[28]	JUPITER 2008[29]
						revasc	death, resuscitated cardiac arrest), coronary revascularization, stroke	cardiac arrest, worsening unstable angina		
Relative risk reduction of primary endpoint	31	37	10	Not significant (p=0.88)	36	33	37	Not significant (p=0.34)	33	44

*Primary prevention subgroup used
†Median; in ASCOT-LLA data were from extended observations trial
‡Data from baseline characteristics publication of PROSPER

JUPITER

Study objectives

The primary objective of JUPITER was to compare the rate of first major cardiovascular events (MCEs) defined as the composite endpoint of cardiovascular death, non-fatal stroke, non-fatal MI, hospitalization for unstable angina, or arterial revascularization in subjects with low LDL levels (<130 mg/dL) and elevated CRP (≥ 2.0 mg/L) on rosuvastatin 20 mg versus placebo.

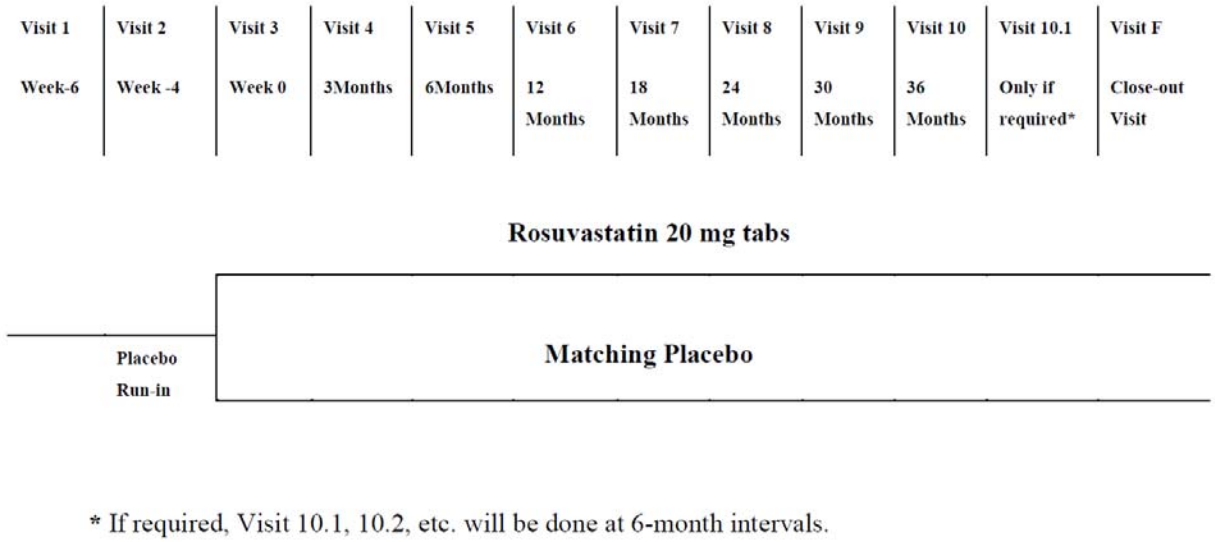
The secondary objectives of JUPITER were to assess safety by comparing total mortality, non-cardiovascular mortality, and adverse events between rosuvastatin and placebo groups. The incidence of diabetes mellitus, venous thromboembolic events, and bone fractures between treatment groups was also assessed.

Study Design

JUPITER was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase 3 trial at 1315 sites in 26 countries comparing 20 mg of rosuvastatin to placebo for the primary prevention of MCEs. The original protocol planned to follow subjects for approximately 3.5 years to accrue the 520 clinical endpoints upon which the study was powered. At the time of a subject's first cardiovascular event, blinded study therapy was to be discontinued. The subject was to continue scheduled study assessments until study conclusion and be treated according to the investigator.

The study was composed of two parts, a 4-week placebo run-in period, followed by a randomized treatment period (Figure 2). A minimum of 10 study visits were planned. After randomization follow-up visits were scheduled at 13 weeks and then at 6 month intervals. Subjects who completed Visit 10 but had not reached a study endpoint were followed at 6 month intervals to repeat assessments done during Visit 9. Once the study closed, all subjects attended a final clinic visit (Visit F).

Figure 2: JUPITER study flow chart



* If required, Visit 10.1, 10.2, etc. will be done at 6-month intervals.

Inclusion criteria of importance

1. Men ≥ 50 years, Women ≥ 60 years
2. Fasting LDL <130 mg/dL
3. hsCRP ≥ 2.0 mg/L
4. Triglycerides <500 mg/dL

Exclusion criteria of importance

1. Treatment with any statin or other lipid lowering therapies within 6 weeks of Screening Visit 1
2. Prior history of cardiovascular or cerebrovascular events such as MI, unstable angina, prior arterial revascularization, or stroke, or CHD risk equivalent as defined by NCEP ATP-III
3. Current use of postmenopausal oral hormone replacement therapy
4. ALT >2x upper limit of normal (ULN)
5. Creatinine kinase > 3x ULN
6. Creatinine >2.0 mg/dL
7. Diabetes mellitus, defined by fasting serum glucose >126 mg/dL or by use of insulin and/or an oral hypoglycemic agent
8. Uncontrolled hypertension, systolic BP >190 mmHg or a diastolic BP >100 mmHg
9. History of malignancy within the past 5 years (exception of basal cell or squamous cell carcinoma of the skin)
10. Uncontrolled hypothyroidism (TSH >1.5x ULN)
11. Chronic inflammatory conditions such as severe arthritis, lupus, or inflammatory bowel disease
12. Treatment with immunosuppressants

Study methods

Procedures for endpoint adjudication

All reported primary endpoints were independently adjudicated by the Clinical Events Committee (CEC) using predefined endpoint criteria (Appendix A). Only events occurring before 31 March 2008 (official study close) that were adjudicated and confirmed as major cardiovascular events were included in the primary efficacy analysis. In cases where the data were insufficient to adjudicate, the event was not considered in the primary efficacy analysis but was included in the assessment of total mortality.

Statistical analysis plan

The intent-to-treat principle was used in the primary analysis of primary and secondary variables. The sponsor controlled for multiplicity for three secondary variables. The following variables were tested in sequential order after establishing statistical significance in the primary efficacy analysis, each at a 5% level of significance:

- CV death, non-fatal stroke or non-fatal MI
- Fatal or non-fatal MI
- Fatal or non-fatal stroke

Hazard ratios and 95% confidence intervals were calculated for event rates between the treatment groups using Cox proportional-hazard models.

The Independent Data Monitoring Board (IDMB) for JUPITER had prespecified interim analyses to occur after 37.5%, 75%, and 100% of primary events had occurred. A group sequential design was used to preserve the overall type 1 error probability of 0.05 (false positive efficacy result). The group sequential boundaries for the three scheduled analyses were 2.947, 2.411, and 2.011, which corresponded to nominal p-values of 0.003, 0.016 and 0.044, respectively. The study was to be terminated early if both the IDMB and steering committee agreed based on safety or efficacy data available at the time of their interim review. The first IDMB meeting recommended continuation of the study with an additional meeting in 6 months. The IDMB convened 6 months later on 29 March 2008 and reviewed unblinded safety and efficacy data. At that time, 328 primary endpoints had been confirmed. On the basis of their review, the IDMB recommended stopping the study early based on evidence of treatment benefit in the rosuvastatin group.

Demographics and other subject characteristics

Twenty six countries participated in JUPITER. The study was originally intended to be performed solely in the United States. However, due to poor recruitment, Canadian sites were added in 2003 and expansion to additional countries was approved in October 2004. In 2004, the age inclusion criterion was lowered from ≥ 55 years in men and ≥ 65 years in women to ≥ 50 years in men and ≥ 60 years in women to enhance recruitment.

The largest number of randomized patients was from the United States, followed by the United Kingdom, South Africa, and Canada. Of the total randomized population 22.6% were from the United States.

In JUPITER, overall there were no significant differences between treatment groups for demographics and baseline characteristics. The majority of subjects enrolled were Caucasian males; approximately 38% were women, and the mean age was 66 years old.

At baseline, the majority of subjects had hypertension (57%) defined as a BP ≥140/90 or on anti-hypertensive medication; smokers comprised 16% of the population; almost a third (31%) of subjects met the definition for impaired fasting glucose (fasting serum glucose ≥100 mg/dl); 12% had a family history of coronary heart disease; 76% were overweight (BMI >25 kg/m^2); and 41% met the criteria for metabolic syndrome.

Calculation of the Framingham risk score at baseline categorized 41% of subjects as low risk (10-year CHD risk <10%), 50.6% as intermediate risk (10-year CHD risk 10-20%), and 8.8% as high risk (10-year CHD risk >20%).

Table 4: JUPITER: Demographics and baseline characteristics (ITT population)

	ITT population N=17802		
	Rosuvastatin 20 mg (N=8901)	**Placebo (N=8901)**	**Total (N=17802)**
Sex, n (%)			
Male	5475 (61.5)	5526 (62.1)	11001 (61.8)
Female	3426 (38.5)	3375 (37.9)	6801 (38.2)
Age (years)			
Mean	66.0 (7.64)	66.0 (7.79)	66.0 (7.71)
Median	66.0	66.0	66.0
Range	49 to 94	50 to 97	49 to 97
Race, n (%)			
Caucasian	6358 (71.4)	6325 (71.1)	12683 (71.2)
Black	1100 (12.4)	1124 (12.6)	2224 (12.5)
Asian	147 (1.7)	136 (1.5)	283 (1.6)
Hispanic	1121 (12.6)	1140 (12.8)	2261 (12.7)
Other	173 (1.9)	176 (2.0)	349 (2.0)
Not recorded	2 (<0.1)	0	2 (<0.1)
Age group at entry, n (%) **Males**			
<50 years	1 (<0.1)	0	1 (<0.1)
50-64 years	3044 (55.6)	3144 (56.9)	6188 (56.2)
65-74 years	1838 (33.6)	1722 (31.2)	3560 (32.4)
75+ years	592 (10.8)	660 (11.9)	1252 (11.4)
Age group at entry, n (%) **Females**			
<60 years	1 (<0.1)	1 (<0.1)	2 (<0.1)
60-74 years	2755 (80.4)	2733 (81.0)	5488 (80.7)
75-84 years	618 (18.0)	572 (16.9)	1190 (17.5)
85+ years	52 (1.5)	69 (2.0)	121 (1.8)
Body mass index, kg/m^2			
Mean (SD)	29.1 (6.69)	29.0 (5.67)	29.0 (6.20)
BMI >25 kg/m^2, n (%)	6826 (76.7)	6839 (76.8)	13665 (76.8)

	ITT population N=17802		
	Rosuvastatin 20 mg (N=8901)	**Placebo (N=8901)**	**Total (N=17802)**
Systolic BP, mmHg			
Mean (SD)	135.6 (16.75)	135.6 (16.79)	135.6 (16.77)
Median	134.0	134.0	134.0
Diastolic BP, mmHg			
Mean (SD)	80.7 (9.09)	80.7 (8.96)	80.7 (9.02)
Median	80.0	80.0	80.0
Current smoking (last month), n (%)	1400 (15.7)	1420 (16.0)	2820 (15.8)
Hypertension, n (%)	5079 (57.1)	5129 (57.6)	10208 (57.3)
Family history of CHD, n (%)	997 (11.2)	1048 (11.8)	2045 (11.5)
Family history of stroke, n (%)	1792 (20.1)	1873 (21.0)	3665 (20.6)
Family history of diabetes, n (%)	2069 (23.2)	2101 (23.6)	4170 (23.4)
FSG ≥ 100 mg/dL, n (%)	2755 (31.0)	2817 (31.6)	5572 (31.3)
Metabolic syndrome[a], n (%)	3652 (41.0)	3725 (41.8)	7377 (41.4)
Framingham risk score			
Mean (SD)	11.6 (7.0)	11.6 (6.9)	11.6 (7.0)
Framingham risk category, n (%)			
Low	3615 (40.6)	3602 (40.5)	7217 (40.5)
Intermediate	4485 (50.4)	4516 (50.7)	9001 (50.6)
High	786 (8.8)	772 (8.7)	1558 (8.8)
Not calculable	15 (0.2)	11 (0.1)	26 (0.1)
eGFR, mL/min/1.73m^2			
Mean (SD)	75.4 (17.5)	75.4 (17.3)	75.4 (17.4)
Median	73.3	73.6	73.6
Range	27-206	21-181	21-206

[a] Subjects had metabolic syndrome if they had 3 or more of the following 5 factors: 1) Waist circumference >40 in (men) or >35 in (women), 2) TG ≥150 mg/dL, 3) HDL-C <40 mg/dL (men) or <50 mg/dL (women), 4) Diastolic blood pressure ≥85 mmHg or systolic blood pressure ≥130 mmHg; or taking prescribed medication for hypertension, 5) Fasting blood glucose ≥100 mg/dL (5.6 mmol/L)
Source: Applicant's Table 12, Pg 54, Table 13, Pg 56 JUPITER CSR

The following table lists the frequency of individual risk factors occurring in JUPITER subjects at baseline as defined by NCEP ATP-III guidelines. The next tables (Table 6 and 7) list the total number of risk factors before and after subtracting 1 risk factor for a HDL-C ≥ 60 mg/dL. Approximately 25% of all subjects had HDL-C ≥ 60 mg/dL. All subjects met the ATP-III age risk criterion, per protocol. When adjusted for high HDL-C values, approximately 60% of subjects had 2 or more conventional risk factors by NCEP ATP-III guidelines.

Table 5: JUPITER: Major cardiovascular NCEP-ATP III risk factors at baseline (ITT population)

Major risk factor	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)	Total N=17802 n (%)
Smoking (last month)	1400 (15.7)	1420 (16.0)	2820 (15.8)
Hypertension (BP ≥140/90 or on antihypertensives)	5079 (57.1)	5129 (57.6)	10208 (57.3)
Low HDL-C (<40 mg/dL)	1980 (22.2)	2023 (22.7)	4003 (22.5)
Family history of premature CHD	997 (11.2)	1048 (11.8)	2045 (11.5)
Age (men ≥45, women ≥55)	8901 (100.0)	8901 (100.0)	17802 (100.0)
HDL ≥ 60 mg/dL	2226 (25.0)	2241 (25.2)	4467 (25.1)
Source: Applicant's Table 11.1.1.3.1.1.1, Pg 278, CSR			

Table 6: JUPITER: Number of cardiovascular risk factors at baseline (ITT population)

Total number of risk factors	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)	Overall N=17802 n (%)
1 risk factor (age only)	2199 (24.7)	2080 (23.4)	4279 (24.0)
2 risk factors	4373 (49.1)	4423 (49.7)	8796 (49.4)
3 risk factors	1931 (21.7)	2017 (22.7)	3948 (22.2)
4 risk factors	371 (4.2)	361 (4.1)	732 (4.1)
5 risk factors	27 (0.3)	20 (0.2)	47 (0.3)
Source: Applicant's Table 11.1.1.3.1.2.1, Pg 287, CSR			

Table 7: JUPITER: Number of cardiovascular risk factors at baseline adjusted for HDL ≥60 mg/dL

Total number of risk factors	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)	Overall N=17802 n (%)
0 risk factors[a]	725 (8.1)	680 (7.6)	1405 (7.9)
1 risk factor	2679 (30.1)	2640 (29.7)	5319 (29.9)
2 risk factors	3451 (38.8)	3487 (39.2)	6938 (39.0)
3 risk factors	1661 (18.7)	1730 (19.4)	3391 (19.0)
4 risk factors	358 (4.0)	344 (3.9)	702 (3.9)
5 risk factors	27 (0.3)	20 (0.2)	47 (0.3)
[a] All subjects with 0 risk factors had HDL-C ≥ 60 mg/dL Source: Applicant's Table 11.1.1.3.1.1.1, Pg 278, CSR			

There were no significant differences in baseline lipoprotein and hsCRP levels between treatment groups. Approximately 29% of JUPITER subjects had hsCRP ≤3 mg/L and the median value for all JUPITER subjects was 4.3 mg/L. As has been reported in the literature, hsCRP in women was slightly higher than in men.[30] Baseline lipoprotein and hsCRP levels are summarized by treatment group in the following table. Values are listed as means unless otherwise noted.

[30] Khera et al. Race and gender differences in C-reactive protein levels. JACC 2005; 46:464-69.

Table 8: JUPITER: Baseline lipoprotein and hsCRP levels (ITT population)

	Rosuvastatin 20 mg N=8901		Placebo N=8901		Overall N=17802
	N	**mg/dL (SD)**	**N**	**mg/dL (SD)**	**mg/dL (SD)**
Total cholesterol	8899	183 (24.7)	8901	183 (24.2)	183 (24.4)
Triglycerides, MEDIAN	8899	118 (73.4)	8901	118 (73.5)	118 (73.4)
HDL-C	8899	51 (15.3)	8901	51 (15.2)	51 (15.3)
LDL-C	8899	104 (18.9)	8899	105 (18.5)	104 (18.7)
Apolipoprotein A-I	8863	166 (31.0)	8857	165 (30.5)	165 (30.7)
Apolipoprotein B	8861	109 (21.7)	8856	109 (21.0)	109 (21.4)
	N	**mg/L (SD)**	**N**	**mg/L**	**mg/L**
hsCRP,	8901	6.6 (8.6)	8901	6.9 (9.2)	6.8 (8.9)
hsCRP minimum		1.1		0.55	0.55
hsCRP maximum		192.0		174.5	192.0
hsCRP, MEDIAN	**N**	**mg/L**	**N**	**mg/L**	**mg/L**
Men and women	8901	4.2	8901	4.3	4.3
Men	5475	4.0	5526	4.1	4.1
Women	3426	4.6	3375	4.7	4.6
	N	**%**	**N**	**%**	**N (%)**
Baseline CRP ≤ 3 mg/L	2649	29.8	2564	28.8	5213 (29.3)

Source: Applicant's Table 17, Table 11.2.2.1.3.1, Pg 3014, CSR JUPITER Table 12.1.9.1.4.2, Pg 710 Appendix 12.1.9

Approximately a third of JUPITER subjects at baseline were taking concomitant cardiovascular medications, the majority of which targeted hypertension. Thiazide diuretics (11.9%), ACE inhibitors (11.0%), and aspirin (10.2%) were the top three concomitant medications at baseline. At baseline, a slightly higher proportion of rosuvastatin-treated subjects were on thiazides compared to placebo-treated subjects. More placebo-treated subjects at baseline were on ACE inhibitors compared to rosuvastatin-treated subjects. Concomitant aspirin medication was balanced between treatment groups at baseline.

Table 9: JUPITER: Concomitant diabetic/cardiovascular medications at baseline (ITT population)

Concomitant diabetic/cardiovascular medications	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)	Total N=17802 n (%)
Diabetic medications: Any	9 (0.1)	12 (0.1)	21 (0.1)
Metformin only	7 (0.1)	8 (0.1)	15 (0.1)
Sulfonylurea only	0	2 (<0.1)	2 (<0.1)
Metformin +sulfonylurea	1 (<0.1)	0	1 (<0.1)
Other antidiabetic	1 (<0.1)	2 (<0.1)	3 (<0.1)
Cardiovascular medications: Any	3004 (33.7)	3035 (34.1)	6039 (33.9)
Antiplatelets (excluding aspirin)	4 (<0.1)	6 (0.1)	10 (0.1)
Aspirin	898 (10.1)	918 (10.3)	1816 (10.2)
ACE inhibitors	955 (10.7)	998 (11.2)	1953 (11.0)
Beta-blockers	793 (8.9)	751 (8.4)	1544 (8.7)
Nitrates	30 (0.3)	30 (0.3)	60 (0.3)

Concomitant diabetic/cardiovascular medications	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)	Total N=17802 n (%)
Calcium channel blockers	597 (6.7)	594 (6.7)	1191 (6.7)
Thiazide diuretics	1082 (12.2)	1038 (11.7)	2120 (11.9)
Loop diuretics	263 (3.0)	279 (3.1)	542 (3.0)
Fibrates	1 (<0.1)	2 (<0.1)	3 (<0.1)
ARBs	590 (6.6)	630 (7.1)	1220 (6.9)
Alpha blocker	319 (3.6)	343 (3.9)	662 (3.7)
Potassium sparing diuretic	202 (2.3)	201 (2.3)	403 (2.3)
Cardiac glycosides	43 (0.5)	56 (0.6)	99 (0.6)
Statin other than CRESTOR	9 (0.1)	15 (0.2)	24 (0.1)
Source: Appendix A, Table 1, Pg 11 IR response 01 September 2009			

Table 10: JUPITER: Concomitant diabetic/cardiovascular medications post-baseline (ITT population)

Concomitant diabetic/cardiovascular medications	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)	Total N=17802 n (%)
Diabetic medications: Any	202 (2.3)	194 (2.2)	396 (2.2)
Metformin only	124 (1.4)	136 (1.5)	260 (1.5)
Sulfonylurea only	21 (0.2)	8 (0.1)	29 (0.2)
Metformin +sulfonylurea	6 (0.1)	7 (0.1)	13 (0.1)
Insulin only	16 (0.2)	15 (0.2)	31 (0.2)
Insulin+metformin+sulfonylurea	2 (<0.1)	3 (<0.1)	5 (<0.1)
Other antidiabetic	33 (0.4)	25 (0.3)	58 (0.3)
No antidiabetic drug treatment following investigator-reported diabetes	76 (0.9)	59 (0.7)	135 (0.8)
Cardiovascular medications: Any	2366 (26.6)	2633 (29.6)	4999 (28.1)
Antiplatelets (excluding aspirin)	22 (0.2)	35 (0.4)	57 (0.3)
Aspirin	674 (7.6)	793 (8.9)	1467 (8.2)
ACE inhibitors	665 (7.5)	714 (8.0)	1379 (7.7)
Beta-blockers	477 (5.4)	600 (6.7)	1077 (6.0)
Nitrates	124 (1.4)	136 (1.5)	260 (1.5)
Calcium channel blockers	405 (4.6)	482 (5.4)	887 (5.0)
Thiazide diuretics	561 (6.3)	644 (7.2)	1205 (6.8)
Loop diuretics	314 (3.5)	349 (3.9)	663 (3.7)
Fibrates	17 (0.2)	28 (0.3)	45 (0.3)
ARBs	434 (4.9)	494 (5.5)	928 (5.2)
Alpha blocker	295 (3.3)	360 (4.0)	655 (3.7)
Potassium sparing diuretic	152 (1.7)	142 (1.6)	294 (1.7)
Cardiac glycosides	71 (0.8)	75 (0.8)	146 (0.8)
Statin other than CRESTOR	182 (2.0)	396 (4.4)	578 (3.2)
Source: Appendix B, Table 2, Pg 12 IR response 01 September 2009			

JUPITER Efficacy results

The first subject was enrolled in February 2003 and the last subject was enrolled in December 2006. Of the 89,846 subjects screened, 17,802 (19.8%) subjects were randomized into the JUPITER study. The majority of subjects were excluded at screening due to a LDL-C ≥ 130 mg/dL (52%) and hsCRP <2 mg/dL (36%). In JUPITER, subjects could discontinue study medication and still participate in the study by continuing follow-up visits. Approximately 19% of rosuvastatin-treated subjects and 22% of placebo-treated subjects discontinued study medication. Overall, 7.8% of the rosuvastatin-treated group and 8% of the placebo-treated group withdrew from the study or were lost to follow-up. There was similar treatment compliance in both treatment groups with 85% of subjects being 80% compliant with study medication during the study. Twice as many placebo-treated subjects started open-label statin medication compared to rosuvastatin-treated subjects.

Primary efficacy endpoint

- Time from randomization to first event of any one of the following:
    - cardiovascular death
    - non-fatal stroke
    - non-fatal myocardial infarction
    - unstable angina
    - arterial revascularization

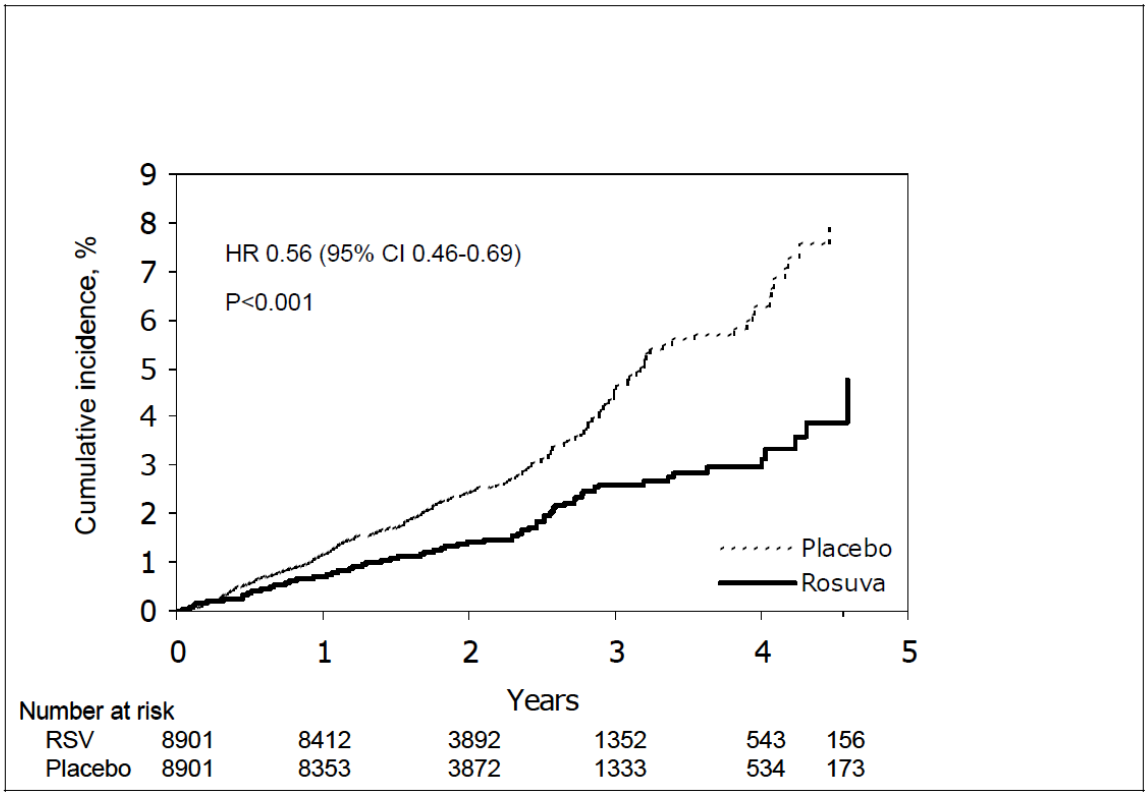
There was a statistically significant difference favoring the rosuvastatin treatment group for this endpoint, as illustrated in the following table and figure:

Table 11: JUPITER: Summary of analysis for primary composite endpoint

Number of Subjects with any Event		Hazard ratio		
Rosuvastatin N=8901 n (%)	**Placebo N=8901 n (%)**	**Estimate**	**95% CI**	**p-value**
142 (1.6)	252 (2.8)	0.56	0.46, 0.69	<0.001
Source: Applicant's Table 18 Pg 62, CSR				

Separation of primary event curves occurred within 6 months of randomization with 32 versus 52 MCEs occurring during this time in the rosuvastatin and placebo treatment groups, respectively, a statistically significant difference by post-hoc analysis (HR 0.62 [95% CI 0.40, 0.96], p=0.029) which continued throughout the study.

Figure 3: JUPITER: Kaplan Meier curve of time to primary composite endpoint



Source: Applicant's Figure 4, Pg 61, CSR

The distribution of the first MCE that contributed to the composite primary endpoint is listed in the table below. Because this analysis was the time to first MCE, this table only shows the first MCE experienced by each subject.

Table 12: Number of events by treatment group for the composite primary endpoint (ITT population)

Endpoint	Rosuvastatin 20 mg N=8901	Placebo N=8901
First MCE	142	252
Cardiovascular death	29	37
Non-fatal MI	21	61
Non-fatal stroke	30	57
Hospitalized unstable angina	15	27
Arterial revascularization	47	70

Source: Applicant's Table 18, Pg 62, CSR JUPITER
[a] Event occurrence counts only 1 MCE for each subject. If subject had more than 1 MCE on the same day, only 1 event is shown in above table, according to the following hierarchy: 1)unstable angina, 2) MI, 3) arterial revascularization, 4) non-fatal stroke, 5) cardiovascular death

The following table shows the frequency of first events for each of the components of the primary composite endpoint, and not just the events that contributed to the composite endpoint. In these analyses subjects were followed until the first occurrence of the specific event, even if the event occurred after a prior non-fatal event. For example, a subject experiencing a non-fatal stroke, followed by a MI would be counted twice, once for stroke and once for MI. The rosuvastatin-treated group experienced a statistically significant reduction in the frequency of

non-fatal strokes, non-fatal MI, and arterial revascularization; however, a statistically significant reduction in the incidence of cardiovascular death and hospitalized unstable angina compared to the placebo group was not seen.

Table 13: JUPITER: Number of first events by treatment group for each individual cardiovascular endpoint (ITT population)

Endpoint	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)	HR	CI for HR	p-value
Cardiovascular death	35 (0.4)	44(0.5)	0.80	0.51, 1.24	0.315
Non-fatal stroke	30 (0.3)	58 (0.7)	0.52	0.33, 0.80	0.003
Non-fatal MI	22 (0.2)	62 (0.7)	0.35	0.22, 0.58	<0.001
Hospitalized unstable angina	16 (0.2)	27 (0.3)	0.59	0.32, 1.10	0.093
Arterial revascularization-overall	71 (0.8)	131 (1.5)	0.54	0.41, 0.72	<0.001
Coronary	50 (0.6)	101 (1.1)	0.50	0.35, 0.69	<0.001
Peripheral	17 (0.2)	28 (0.3)	0.61	0.33, 1.12	0.105
Carotid	6 (0.1)	4 (<0.1)	1.52	0.43, 5.37	0.515

[a] Not limited to the first occurrence of a MCE
Source: Applicant's Table 19, Pg 63, CSR

Time to cardiovascular death/MI/stroke

Although the study was not powered for the individual components of the primary composite endpoint, an amendment to the statistical analysis plan introduced three secondary variables to support the primary efficacy endpoint. If the primary composite endpoint was statistically significant then in sequential order, at a level of 5% significance, the following variables were tested using adjudicated events.

1. Cardiovascular death, non-fatal stroke, or non-fatal MI
2. Fatal or non-fatal MI
3. Fatal or non-fatal stroke

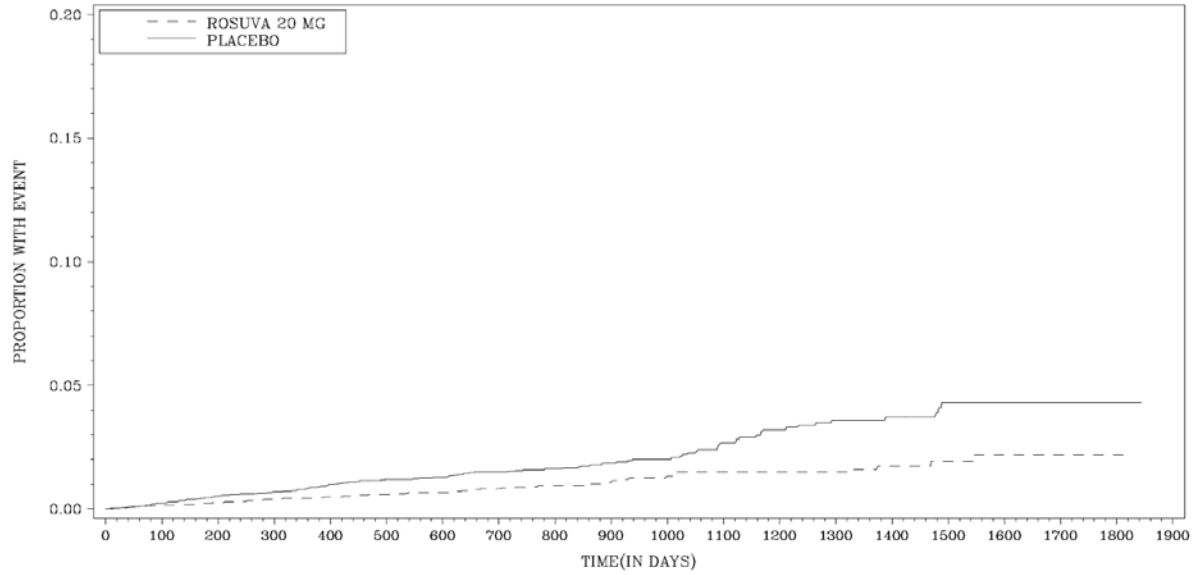
The following table lists these analyses as well as the cardiovascular death individual component analysis for reference.

Table 14: JUPITER: Other cardiovascular efficacy endpoints (ITT population)

	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)	HR (95% CI)	p-value
CV death/MI/stroke	83 (0.9)	158 (1.8)	0.52 (0.40, 0.68)	<0.001
Fatal or non-fatal MI	31 (0.3)	68 (0.8)	0.46 (0.30, 0.70)	<0.001
Fatal or non-fatal stroke	33 (0.4)	64 (0.7)	0.52 (0.34, 0.79)	0.002
Cardiovascular death	35 (0.4)	44 (0.5)	0.80 (0.51, 1.24)	0.315

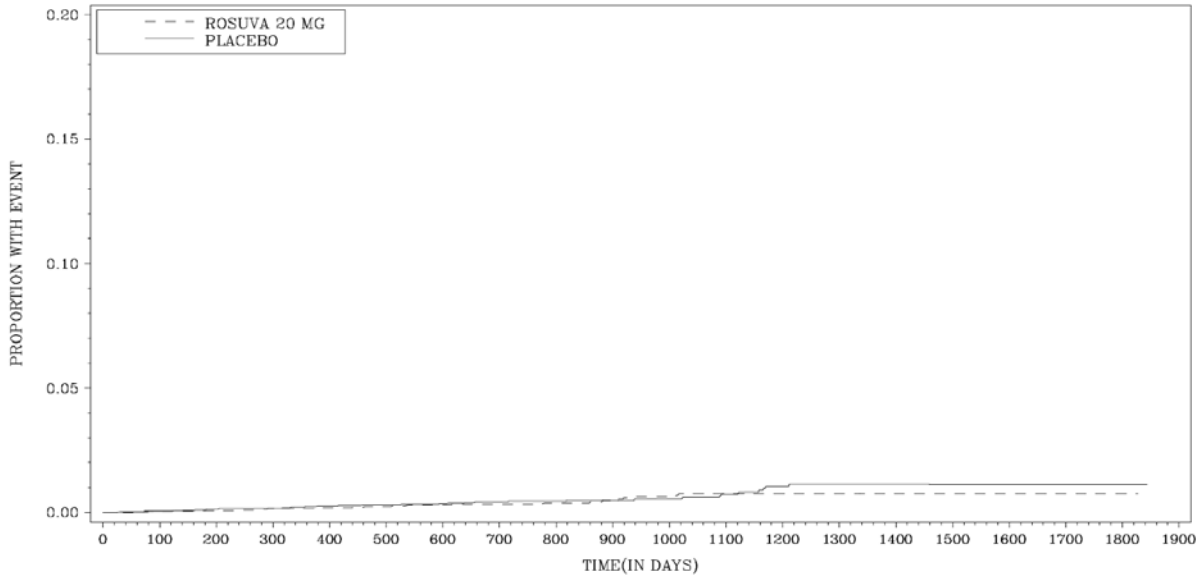
Source: Applicant's Table 22, Pg 67, CSR

Figure 4: JUPITER: Kaplan-Meier plot of time to CV death, MI or stroke (Adjudicated events) ITT population



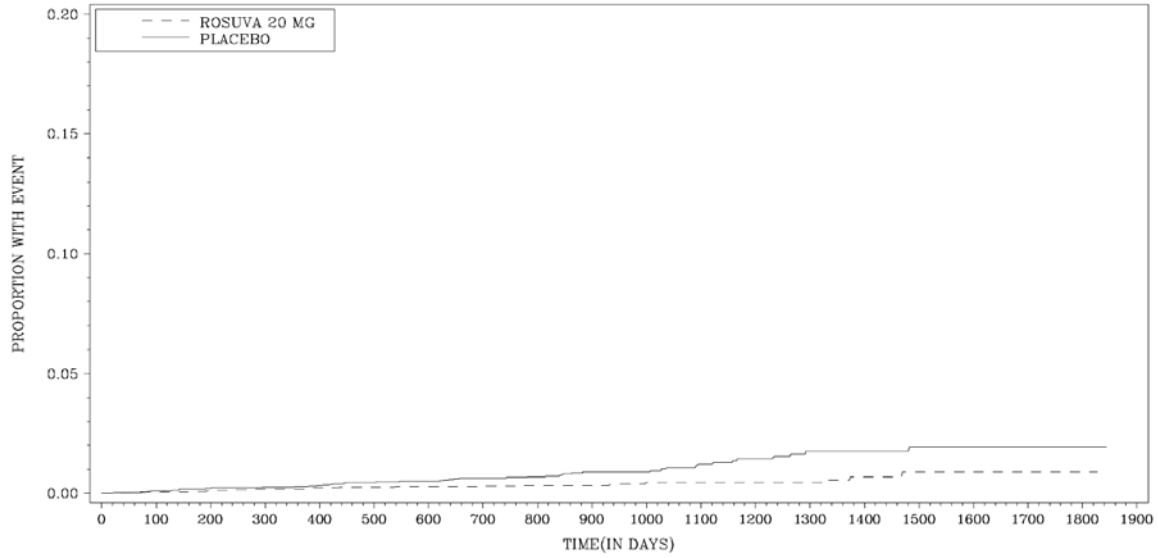
Source: Applicant's Figure 11.2.1.2.3, Pg 2831, CSR

Figure 5: JUPITER: Kaplan-Meier plot of time to CV death (Adjudicated events) ITT population



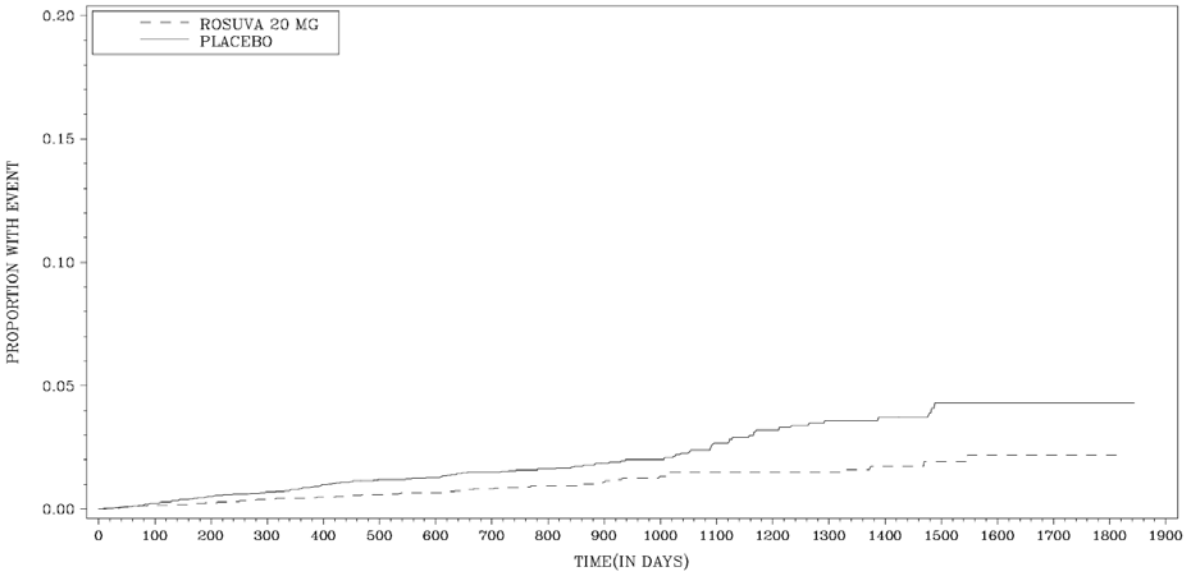
Source: Applicant's Figure 11.2.1.10.3, Pg 2855, CSR

Figure 6: JUPITER: Kaplan-Meier plot of time to fatal/non-fatal MI (Adjudicated events) ITT population



Source: Applicant's Figure 11.2.1.3.3, Pg 2836, CSR

Figure 7: JUPITER: Kaplan-Meier time to fatal/non-fatal stroke (Adjudicated events) ITT population



Source: Applicant's Figure 11.2.1.4.3, Pg 2839, CSR

Prespecified subgroup analyses

In general, the treatment effect of rosuvastatin on the primary endpoint was consistent across prespecified subgroups (Table 15). All hazard ratios favored the rosuvastatin-treated group.

Table 15: JUPITER: Time to primary composite endpoint among prespecified subgroups

	Rosuvastatin		Placebo			
Subgroup	**N**	**n (rate/1000 pt years)**	**N**	**n (rate/1000 pt years**	**Hazard ratio (95% CI)**	**p-value for interaction**
AGE						
≤ 65 years at baseline	4216	42 (4.9)	4325	90 (10.3)	0.48 (0.33, 0.69)	0.338
>65 years at baseline	4685	100 (9.9)	4576	162 (16.6)	0.60 (0.47, 0.76)	
SEX						
Males	5475	103 (8.8)	5526	182 (15.5)	0.57 (0.45, 0.73)	0.817
Females	3426	39 (5.6)	3375	70 (10.4)	0.54 (0.37, 0.80)	
AGE BY SEX						
Male <65 y, Female < 75 y	5762	55 (4.7)	5837	120 (10.1)	0.46 (0.34, 0.64)	0.128
Males≥65 y, Female≥75 y	3139	87 (12.9)	3064	132 (20.1)	0.64 (0.49, 0.84)	
RACE						
Caucasian	6358	111 (7.8)	6325	202 (14.4)	0.54 (0.43, 0.69)	0.561
Non-Caucasian	2543	31 (7.0)	2576	50 (11.1)	0.63 (0.40, 0.99)	
SMOKER						
No	7496	110 (6.9)	7479	190 (12.1)	0.58 (0.46, 0.73)	0.644
Yes	1400	32 (11.7)	1420	62 (22.6)	0.51 (0.34, 0.79)	
BODY MASS INDEX						
BMI ≤ 30	5535	94 (8.2)	5547	179 (15.9)	0.52 (0.40, 0.67)	0.313
BMI >30	3339	47 (6.6)	3336	73 (10.2)	0.65 (0.45, 0.94)	
HDL-C						
HDL <40 mg/dL	1980	32 (7.6)	2023	65 (15.3)	0.50 (0.33, 0.76)	0.512
HDL ≥40 mg/dL	6919	110 (7.7)	6878	187 (13.1)	0.58 (0.46, 0.74)	
LDL-C						
≤100 mg/dL	3118	55 (8.7)	3153	86 (13.5)	0.65 (0.46, 0.91)	0.304
>100 mg/dL	5781	87 (7.1)	5746	166 (13.7)	0.52 (0.40, 0.67)	
Above median[a]	4571	68 (7.0)	4628	138 (14.1)	0.50 (0.37, 0.67)	0.236

	Rosuvastatin		Placebo			
Subgroup	**N**	**n (rate/1000 pt years)**	**N**	**n (rate/1000 pt years**	**Hazard ratio (95% CI)**	**p-value for interaction**
Below median	4328	74 (8.3)	4271	114 (13.1)	0.64 (0.48, 0.86)	
TRIGLYCERIDES						
<200 mg/dL	7398	117 (7.6)	7384	208 (13.6)	0.56 (0.45, 0.71)	0.974
≥200 mg/dL	1501	25 (7.7)	1517	44 (13.7)	0.56 (0.34, 0.91)	
HTN						
Yes	5079	89 (8.5)	5129	166 (15.8)	0.54 (0.42, 0.70)	0.559
No	3818	53 (6.6)	3768	86 (10.8)	0.61 (0.43, 0.86)	
REGION						
US	1990	58 (10.7)	2031	94 (16.9)	0.63 (0.45, 0.87)	0.395
Countries other than US	6911	84 (6.4)	6870	158 (12.2)	0.52 (0.40, 0.68)	
US or Canada	3007	81 (9.7)	3034	137 (16.3)	0.60 (0.45, 0.78)	0.536
Countries other than US/Canada	5894	61 (6.0)	5867	115 (11.4)	0.52 (0.38, 0.71)	
METABOLIC SYNDROME						
No	5218	75 (6.9)	5146	149 (14.0)	0.50 (0.38, 0.66)	0.167
Yes	3652	67 (8.7)	3725	102 (13.1)	0.67 (0.49, 0.91)	
BASELINE hsCRP						
Above median[a]	4446	89 (9.7)	4551	128 (13.7)	0.71 (0.54, 0.92)	0.015
Below median	4454	53 (5.6)	4350	124 (13.5)	0.42 (0.30, 0.58)	
≤4 mg/L	4211	50 (5.6)	4113	119 (13.8)	0.41 (0.30, 0.57)	0.014
>4 mg/L	4689	92 (9.5)	4788	133 (13.5)	0.70 (0.54, 0.91)	
Baseline LDL-C and hsCRP						
Below median LDL-C and hsCRP	2072	24 (5.6)	1988	47 (11.3)	0.50 (0.30, 0.81)	0.094
Above median LDL-C and below median hsCRP	2382	29 (5.7)	2361	77 (15.3)	0.37 (0.24, 0.57)	
Above median LDL-C and hsCRP	2189	39 (8.5)	2267	61 (12.8)	0.66 (0.44, 0.99)	
Below median LDL-C and above median hsCRP	2256	50 (10.9)	2283	67 (14.7)	0.74 (0.51, 1.07)	
Baseline fasting serum glucose						
<100 mg/dL	6120	87 (6.9)	6061	167 (13.3)	0.52 (0.40, 0.67)	0.257
≥100 mg/dL	2755	55 (9.4)	2817	84 (14.2)	0.66 (0.47, 0.93)	

	Rosuvastatin		Placebo			
Subgroup	**N**	**n (rate/1000 pt years)**	**N**	**n (rate/1000 pt years**	**Hazard ratio (95% CI)**	**p-value for interaction**
[a] Median baseline LDL-C was 108 mg/dL; median hsCRP was 4.25 mg/L Applicant's Table 12.1.9.1.4.1, Pg 699, Appendix 12.1.9						

Post-hoc exploratory subgroup analyses

Additional post-hoc subgroup analyses were done with regard to baseline hsCRP, cardiovascular risk scores, and number of risk factors.

Table 16: JUPITER: Time to primary composite endpoint among post-hoc subgroups

	Rosuvastatin		Placebo			
Subgroup	**N**	**n events (rate/1000 pt years)**	**N**	**n events (rate/1000 pt years**	**Hazard ratio (95% CI)**	**p-value for interaction**
Baseline CRP						
≤3 mg/L	2649	31 (5.6)	2564	70 (13.0)	0.43 (0.28, 0.66)	0.141
>3 mg/L	6252	111 (8.5)	6337	182 (13.9)	0.62 (0.49, 0.78)	
Number of risk factors						
<2	2199	33 (7.1)	2080	35 (7.9)	0.91 (0.56, 1.46)	0.034
≥2	6702	109 (7.8)	6821	217 (15.5)	0.51 (0.40, 0.64)	
Framingham risk scores						
<10% (low risk)	3615	29 (4.0)	3602	43 (6.0)	0.67 (0.42, 1.07)	0.945
10-20% (intermediate risk)	4485	83 (8.6)	4516	171 (17.6)	0.49 0.38, 0.64)	
>20% (high risk)	786	29 (17.2)	772	38 (24.1)	0.70 (0.43, 1.14)	
Applicant's Table 12.1.9.1.4.2, Pg 710, Appendix 12.1.9						

Analysis of secondary endpoints

- Time from randomization to first occurrence of:
    - Death (total mortality)
    - Non-cardiovascular mortality
    - Development of diabetes mellitus
    - Development of venous thromboembolic events (deep vein thrombosis or pulmonary embolism)
    - Bone fractures

Time to death (total mortality)

Time to death was collected from deaths that occurred during the study and through external data sources such as public death records which provided only vital status. In JUPITER, using all

information available on vital status, there were a total of 445 deaths, 198 in rosuvastatin-treated subjects and 247 in placebo-treated subjects. When external data sources were excluded there were a total of 372 deaths, 167 in rosuvastatin and 205 in placebo treatment groups. The analysis including external data sources reached statistical significance and there was a trend towards significance when external vital status was omitted.

Table 17: JUPITER: Number of events by treatment group time to death (total mortality) with and without external vital status data (ITT population)

	Number of events (% of subjects having an event)						
	Rosuvastatin 20 mg N=8901		Placebo N=8901				
	n	%	n	%	HR	95% CI	p-value
All-cause death (including external vital status)	198	2.2	247	2.8	0.80	0.67, 0.97	0.021
All-cause death (excluding external vital status)	167	1.9	205	2.3	0.82	0.67, 1.00	0.051
Source: Applicant's Table 11.2.1.18.1, Pg 2877, Table 11.2.1.19.1, Pg 2880, CSR							

Other secondary endpoints

A 16% reduction in risk of non-cardiovascular death in rosuvastatin subjects was observed in JUPITER. This treatment difference, however, did not reach statistical significance. There was a significant treatment effect favoring rosuvastatin in the time to development of venous thromboembolic events (VTE) which was defined as either a deep vein thrombosis or pulmonary embolism. In JUPITER, there was similar incidence of fracture in both the rosuvastatin and placebo treatment groups.

Table 18: JUPITER: Summary and time to development of other secondary endpoints

	Number of events (% of subjects having an event)						
	Rosuvastatin 20 mg N=8901		Placebo N=8901				
	n	%	n	%	HR	95% CI	p-value
Non-cardiovascular death	105	1.2	126	1.4	0.84	0.65, 1.08	0.172
Venous thromboembolic events	26	0.3	46	0.5	0.57	0.35, 0.91	0.018
New bone fractures-total	226	2.5	214	2.4	1.06	0.88, 1.28	0.548
Source: Applicant's Table 11.2.1.20.1-2, Pg 2883-4, Table- 11.2.1.23.1, 2 Pg 2892-4; Table 11.2.1.26.1-2 Pg 2902-3, CSR JUPITER							

Time to development of (investigator-reported) diabetes mellitus

There was more investigator-reported diabetes in the rosuvastatin-treated group (251/8901, 2.8%) versus the placebo-treated (205/8901, 2.3%) group. This endpoint is discussed further in the Safety section.

Lipoprotein and hsCRP values

Levels of lipoproteins and hsCRP values were similar at baseline between treatment groups and are summarized at baseline, 1 year, and at the Final visit in Table 19. As expected, compared to

the placebo group there was a significant increase in HDL-C and decrease in all other lipoproteins and hsCRP levels on rosuvastatin therapy after one year and at the Final visit. After 12 months of rosuvastatin, mean LDL was reduced by 40% in the rosuvastatin group compared to a 5% increase in the placebo group (Table 20). Similarly, mean hsCRP was 13% lower in the rosuvastatin group compared with a 16% increase in the placebo group. The median percent reduction from baseline of hsCRP in the rosuvastatin-treated subjects was 47% compared to 20% among placebo-treated subjects after one year.

Table 19: JUPITER: Summary of lipoproteins and hsCRP values throughout study (ITT population)

	Baseline		After 12 months		At Final visit (LOCF)	
	Rosuvastatin 20 mg	**Placebo**	**Rosuvastatin 20 mg**	**Placebo**	**Rosuvastatin 20 mg**	**Placebo**
TC (mg/dL)						
N	8899	8901	7962	7928	8157	8151
Mean (SD)	183.23 (24.71)	183.39 (24.16)	139.15 (33.31)	188.85 (30.02)	144.02 (35.87)	187.18 (31.24)
Median	186.00	185.00	133.00	188.00	137.00	188.00
Range	76.0-291.0	71.0-340.0	62.0-297.0	76.0-352.0	57.0-327.0	69.0-530.0
HDL-C (mg/dL)						
N	8899	8901	7960	7927	8157	8151
Mean (SD)	51.36 (15.34)	51.26 (15.20)	54.66 (16.33)	52.22 (15.60)	55.36 (17.29)	53.26 (16.50)
Median	49.00	49.00	52.00	50.00	52.00	50.00
Range	11.0-145.0	13.0-145.0	12.0-164.0	10.0-149.0	18.0-165.0	8.0-180.0
LDL-C (mg/dL)						
N	8899	8899	7949	7909	8154	8150
Mean (SD)	104.34 (18.91)	104.57 (18.51)	61.64 (27.57)	109.10 (25.02)	65.72 (30.39)	107.15 (25.99)
Median	108.00	108.00	55.00	110.00	57.00	108.00
Range	12.0-148.0	6.0-170.00	0.0-205.0	6.0-254.0	1.0-245.0	9.0-254.0
TG (mg/dL)						
N	8899	8901	7962	7928	8157	8151
Mean (SD)	137.76 (73.42)	137.80 (73.46)	114.91 (64.90)	138.39 (75.71)	115.25 (68.80)	134.39 (82.07)
Median	118.00	118.0	99.00	119.00	99.00	115.00
Range	19.0-499.0	24.0-496.0	18.0-1385.0	25.0-796.0)	16.0-2146.0	12.0-3150.0
Apo B-100 (mg/dL)						
N	8861	8856	7873	7858	8054	8050
Mean (SD)	108.73 (21.71)	108.72 (21.02)	70.91 (22.17)	105.41 (21.80)	73.32 (24.14)	102.50 (22.34)
Median	109.00	109.00	66.00	105.00	68.00	102.00
Range	28.0-234.0	28.0-222.0	26.0-196.0	27.0-218.0	25.0-234.0	29.0-238.0
Apo A-1 (mg/dL)						
N	8863	8857	7887	7859	8059	8052
Mean (SD)	165.90 (30.95)	164.96 (30.47)	168.01 (32.41)	163.95 (31.01)	166.64 (33.79)	163.56 (33.42)
Median	162.00	162.00	165.00	161.00	163.00	159.00
Range	64.0-331.0	56.0-378.0	42.0-357.0	16.0-325.0	69.0-365.0	5.0-363.0
Apo B-100/Apo A-1 ratio						
N	8861	8856	7873	7857	8054	8050
Mean (SD)	0.68 (0.193)	0.68 (0.190)	0.44 (0.170)	0.67 (0.221)	0.46 (0.181)	0.65 (0.201)
Median	0.66	0.67	0.40	0.65	0.42	0.64

	Baseline		After 12 months		At Final visit (LOCF)	
	Rosuvastatin 20 mg	**Placebo**	**Rosuvastatin 20 mg**	**Placebo**	**Rosuvastatin 20 mg**	**Placebo**
Range	0.1-1.6	0.1-2.4	0.1-1.7	0.2-10.3	0.1-1.5	0.1-4.5
hsCRP (mg/L)						
N	8901	8901	7950	7923	8613	8630
Mean (SD)	6.629 (8.59)	6.923 (9.17)	4.535 (9.86)	6.010 (10.26)	5.213 (10.72)	6.755 (12.051)
Median	4.200	4.300	2.200	3.500	2.600	3.700
Range	1.10-192.0	0.55-174.50	0.10-294.60	0.07-213.00	0.11-294.60	0.200-281.0

Source: Applicant's Table 24 Pg 74, CSR

Table 20 JUPITER: Summary of percent changes from baseline in lipoproteins and hsCRP after 1 year of study treatment and at final visit (ITT population)

	After 12 months		At final visit (LOCF)	
	Rosuvastatin 20 mg	**Placebo**	**Rosuvastatin 20 mg**	**Placebo**
TC				
N	7961	7928	8155	8151
LS Mean (SE)	-23.57 (0.177)	3.30 (0.177)	-20.93 (0.190)	2.44 (0.190)
p-value	<0.001		<0.001	
Difference (95% CI)	-26.87 (-27.36, -26.38)		-23.37 (-23.90, -22.84)	
HDL-C				
N	7959	7927	8155	8151
LS Mean (SE)	7.61 (0.199)	2.98 (0.199)	8.97 (0.211)	4.97 (0.211)
p-value	<0.001		<0.001	
Difference (95% CI)	4.63 (4.08, 5.18)		4.00 (3.42, 4.59)	
LDL-C				
N	7948	7907	8152	8148
LS Mean (SE)	-39.93 (0.292)	5.36 (0.293)	-35.98 (0.310)	3.61 (0.310)
p-value	<0.001		<0.001	
Difference (95% CI)	-45.29 (-46.10, -44.48)		-39.59 (-40.45, -38.72)	
TG				
N	7961	7928	8155	8151
LS Mean (SE)	-9.43 (0.432)	6.80 (0.433)	-8.87 (0.494)	4.92 (0.494)
p-value	<0.001		<0.001	
Difference (95% CI)	-16.23 (-17.43, -15.04)		-13.78 (-15.15, -12.41)	
Apo B-100				
N	7842	7823	8020	8012
LS Mean (SE)	-33.82 (0.205)	-2.07 (0.205)	-31.60 (0.219)	-4.73
p-value	<0.001		<0.001	
Difference (95% CI)	-31.75 (-32.32, -31.18)		-26.86 (-27.47, -26.26)	
Apo A-1				
N	7857	7825	8026	8015
LS Mean (SE)	1.95 (0.154)	-0.08 (0.155)	1.17 (0.167)	-0.34 (0.167)
p-value	<0.001		<0.001	
Difference (95% CI)	2.03 (1.60, 2.46)		1.51 (1.04, 1.97)	
Apo B-100/Apo A-1 ratio				
N	7842	7822	8020	8012
LS Mean (SE)	-33.85 (0.246)	-0.66 (0.246)	-31.08 (0.257)	-2.75 (0.257)
p-value	<0.001		<0.001	
Difference (95% CI)	-33.19 (-33.87, -32.50)		-28.33 (-29.04, -27.61)	
hsCRP				
N	7950	7923	8613	8630
LS Mean (SE)	-12.94 (2.258)	15.65 (2.262)	1.49 (2.432)	27.68 (2.430)
p-value	<0.001		<0.001	
Difference (95% CI)	-28.59 (-34.86, -22.33)		-26.20 (-32.94, -19.46)	
Median % change from baseline (SD)	-46.86 (199.46)	-20.00 (203.18)	-40.91 (220.11)	-13.64 (231.17)

Source: Applicant's Table 25, Pg 75, CSR

JUPITER Efficacy conclusions:

- Treatment with rosuvastatin in subjects with no clinically evident cardiovascular disease, a LDL-C of <130 mg/dL, hsCRP ≥2 mg/L, and at least one other major ATP-III risk factor resulted in a 44% reduction in time to major cardiovascular events defined as the composite of cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, and revascularization.
- The three pre-specified secondary outcomes (a) cardiovascular death/MI/stroke, (b) non-fatal MI/MI, (c) non-fatal stroke/stroke which controlled for Type I error demonstrated a significant reduction in events in the rosuvastatin-treated group compared to the placebo-treated group.
- JUPITER was not powered to detect the statistical significance of individual components of the primary efficacy composite, and cardiovascular death and hospitalization for unstable angina did not reach statistical significance, although the numbers trended in favor of rosuvastatin.
- The analysis for the secondary outcome variable, total mortality did not control for Type 1 error and achieved a nominal p-value of 0.02. When subjects with a Framingham risk score >20% were excluded from the total mortality analysis, the nominal p-value was 0.05.
- A small but significant increase in HDL-C and significant reductions in the other measured lipoproteins and hsCRP were observed in the rosuvastatin group compared to the placebo group.
- In an exploratory post-hoc subgroup analyses of 24% of JUPITER subjects possessing only age as a risk factor and an elevated hsCRP, the HR was 0.91 and 95% CI was 0.56, 1.46.
- In an exploratory post-hoc subgroup analyses, subjects with an intermediate Framingham risk score (10-20%) demonstrated the largest relative risk reduction compared to low and high categories of Framingham risk.

JUPITER Safety Results

Exposure to study drug

In the safety population defined as subjects receiving at least one dose of allocated study medication, the mean exposure was 1.9 years for both the rosuvastatin and placebo treatment groups.

Table 21: JUPITER: Extent of exposure during randomized treatment phase (safety population)

Exposure by duration treatment (days)[a]	Rosuvastatin 20 mg N=8869	Placebo N=8864
Mean (SD)	700.5 (358.19)	689.5 (352.00)
Median	657.0	648.0
Range	0 to 1827	0 to 1967

[a]Duration of treatment calculated as number of days from the day of randomization to date of last dose on the completion/withdrawal page
Source: Applicant's Table 29, Pg 80 CSR JUPITER

Adverse events

The following table provides an overview of the frequency of different categories of treatment-emergent adverse events in JUPITER. The proportion of subjects who had any adverse event, any event leading to death, or discontinuation, or any serious adverse event was similar between the treatment groups.

Table 22: JUPITER: Overview of frequency of treatment-emergent adverse events categories (ITT population)

Event category	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Any adverse event	6968 (78.3)	6907 (77.6)
AE leading to death	141 (1.6)	179 (2.0)
Discontinuations due to AE (DAE)	143 (1.6)	158 (1.8)
Serious AE (SAE)	1341 (15.1)	1372 (15.4)

Source: Applicant's Table 11.3.2.1.2.2, Pg 4587 CSR JUPITER

Treatment-emergent adverse events during the randomized treatment phase

The following table lists the treatment-emergent adverse events (TEAE) by system organ class occurring during the randomized treatment phase of JUPITER. A higher proportion of events occurred in rosuvastatin-treated subjects in the musculoskeletal and connective tissue disorder system organ class compared to placebo-treated subjects due to differences in back pain and myalgia.

Table 23: Treatment-emergent adverse events during the randomized treatment phase (ITT)

System organ class	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Infections and infestations	3873 (43.5)	3941 (44.3)
Musculoskeletal and connective tissue disorders	3293 (37.0)	3037 (34.1)
Gastrointestinal disorders	2231 (25.1)	2209 (24.8)
Respiratory, thoracic, and mediastinal disorders	1445 (16.2)	1429 (16.1)
Nervous system disorders	1424 (16.0)	1492 (16.8)
Injury, poisoning, and procedural complications	1342 (15.1)	1255 (14.1)
General disorders and administration site conditions	1238 (13.9)	1228 (13.8)
Skin and subcutaneous tissue disorders	1106 (12.4)	1145 (12.9)
Vascular disorders	937 (10.5)	1095 (12.3)
Investigations	865 (9.7)	810 (9.1)
Renal and urinary disorders	812 (9.1)	817 (9.2)
Metabolism and nutrition disorders	684 (7.7)	752 (8.4)
Eye disorders	631 (7.1)	665 (7.5)
Psychiatric disorders	625 (7.0)	646 (7.3)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	608 (6.8)	676 (7.6)
Reproductive system and breast disorders	551 (6.2)	602 (6.8)
Cardiac disorders	543 (6.1)	636 (7.1)
Ear and labyrinth disorders	438 (4.9)	452 (5.1)
Blood and lymphatic system disorders	295 (3.3)	292 (3.3)
Hepatobiliary disorders	189 (2.1)	187 (2.1)
Immune system disorders	142 (1.6)	144 (1.6)
Endocrine disorders	100 (1.1)	101 (1.1)
Congenital, familial, and genetic disorders	42 (0.5)	28 (0.3)
Surgical and medical procedures	5 (0.1)	3 (<0.1)
Social circumstances	4 (<0.1)	14 (0.2)
Source: Applicant's Table 32, Pg 82 CSR JUPITER		

The most common treatment-emergent adverse events by preferred term occurring with a frequency of ≥2% in the rosuvastatin treatment group are listed below.

Table 24: The most common treatment-emergent adverse events occurring with a frequency of ≥ 2%

Preferred term	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Urinary tract infection	772 (8.7)	764 (8.6)
Nasopharyngitis	679 (7.6)	642 (7.2)
Back pain	679 (7.6)	616 (6.9)
Myalgia	678 (7.6)	590 (6.6)
Bronchitis	643 (7.2)	631 (7.1)
Upper respiratory tract infection	630 (7.1)	676 (7.6)
Hypertension	624 (7.0)	695 (7.8)
Arthritis	516 (5.8)	495 (5.6)
Cough	475 (5.3)	472 (5.3)
Bone pain	449 (5.0)	451 (5.1)
Diarrhea	417 (4.7)	406 (4.6)

Preferred term	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Influenza	357 (4.0)	324 (3.6)
Sinusitis	356 (4.0)	332 (3.7)
Arthralgia	341 (3.8)	287 (3.2)
Headache	338 (3.8)	356 (4.0)
Edema peripheral	329 (3.7)	263 (3.0)
Fatigue	325 (3.7)	311 (3.5)
Muscle spasms	318 (3.6)	282 (3.2)
Dizziness	308 (3.5)	352 (4.0)
Constipation	294 (3.3)	263 (3.0)
Musculoskeletal pain	281 (3.2)	297 (3.3)
Diabetes mellitus	267 (3.0)	222 (2.5)
Lower respiratory tract infection	254 (2.9)	244 (2.7)
Insomnia	226 (2.5)	208 (2.3)
Abdominal pain	224 (2.5)	227 (2.6)
Rash	219 (2.5)	222 (2.5)
Nausea	218 (2.4)	202 (2.3)
Hematuria	216 (2.4)	181 (2.0)
Dyspepsia	212 (2.4)	226 (2.5)
Pneumonia	199 (2.2)	242 (2.7)
Non-cardiac chest pain	196 (2.2)	209 (2.3)
Pharyngitis	195 (2.2)	198 (2.2)
Anemia	192 (2.2)	183 (2.1)
Pain in extremity	191 (2.1)	183 (2.1)
Gastroesophageal reflux disease	190 (2.1)	226 (2.5)
Depression	184 (2.1)	214 (2.4)
Cataract	180 (2.0)	196 (2.2)
Source: Applicant's Table 11.3.2.1.3.1, Pg 4650 CSR JUPITER		

Deaths

All deaths occurring during the randomized treatment phase of JUPITER were adjudicated by the Clinical Events Committee as either cardiovascular or non-cardiovascular. Adjudicated cardiovascular deaths that occurred before 31 March 2008 were not included as an AE leading to death, but as a primary endpoint. If there were insufficient data to adjudicate a potential cardiovascular death, these events were listed as an AE leading to death and included in the total mortality analysis. There were a total of 320 treatment-emergent AEs leading to death in the JUPITER trial; these are listed below by system organ class (SOC) and treatment group.

Table 25: JUPITER: Treatment-emergent adverse events leading to death by system organ class (ITT population)

System organ class	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Any death	**141 (1.6)**	**179 (2.0)**
Neoplasms benign, malignant and unspecified (includes cysts and polyps)	40 (0.4)	65 (0.7)
General disorders and administration site conditions	39 (0.4)	40 (0.4)
Infections and infestations	22 (0.2)	24 (0.3)
Respiratory, thoracic, and mediastinal disorders	14 (0.2)	20 (0.2)

System organ class	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Gastrointestinal disorders	13 (0.1)	1 (<0.1)
Cardiac disorders	8 (0.1)	8 (0.1)
Injury, poisoning, and procedural complications	3 (<0.1)	8 (<0.1)
Nervous system disorders	3 (<0.1)	4 (<0.1)
Psychiatric disorders	3 (<0.1)	1 (<0.1)
Metabolism and nutrition disorders	2 (<0.1)	0
Vascular disorders	2 (<0.1)	5 (0.1)
Blood and lymphatic system disorders	1 (<0.1)	0
Hepatobiliary disorders	1 (<0.1)	1 (<0.1)
Renal and urinary disorders	1 (<0.1)	4 (<0.1)
Applicant's Table 34, Pg 85 CSR JUPITER		

There was an imbalance noted in treatment-emergent gastrointestinal disorders AEs leading to death with 13 subjects in the rosuvastatin-treated group versus one subject in the placebo-treated group. Source documents were requested and reviewed regarding these gastrointestinal deaths. It was noted that two deaths in the rosuvastatin-treatment group were miscoded. One subject (1280-0011) was reported as dying of gastroesophageal reflux when a subdural hematoma after a fall was the actual cause of death. The other subject (5002-0367) was not confirmed dead but reported as lost to follow-up with the subject's last known location in the hospital. In the rosuvastatin-treatment group two subjects experienced pancreatitis, two subjects experienced peritonitis, and four subjects experienced a fatal gastrointestinal hemorrhage, two of which were associated with either a post-surgical complication or history of alcoholic cirrhosis and esophageal varices. The placebo-treated subject died of peritonitis following gastric bypass surgery.

Table 26: Treatment-emergent adverse events in the Gastrointestinal SOC leading to death

Center	Subject ID	Age	Sex	Preferred term	Days on treatment	Days between AE onset and death	Country	Medications	Comments
Rosuvastatin –treatment group									
1035	0011	62	M	1. Pancreatitis acute 2. Peritonitis	240	3	U.S.	Albuterol, BP meds, ASA, pressors, bicarb, narcotics, hytrin, prednisone	Past medical history: HTN, obesity, chronic DVT Abdominal pain, N/V BP 96/50, lipase 2216, arrested during central line placement, prolonged anuria, ventilator, anoxic encephalopathy

Center	Subject ID	Age	Sex	Preferred term	Days on treatment	Days between AE onset and death	Country	Medications	Comments
1035	0050	83	M	Pancreatitis acute	405	8	U.S.	Advair, prednisone, antibiotics, BP meds, PPI, zofran, insulin, diuretic	Nursing home resident with COPD admitted to hospital with abdominal pain (amylase 195, ULN 5.1mEq/L), new afib, metabolic acidosis (pH 7.2, bicarb 24 mmol/L), Hospital course-dehydration, acute renal failure, multiple electrolyte abnormalities, hyperglycemia
6042	0370	61	F	Peritonitis	294	8	South America	BP med	PMH: HTN,arthritis. Admitted (b) (b) and died (b) (b)
7216	0031	57	M	Gastrointestinal hemorrhage	127	6	Venezuela	Tegretol, mellaril, omeprazole, ranitidine, sucralfate, atenolol	Epigastric pain, coffee ground emesis, melena. Hospitalized (b) (b) (6) Endoscopy: hiatal hernia, esophagitis, Died at home (b) (b) PMH; schizophrenia, HTN
1265	0001	67	M	Intra-abdominal hemorrhage	1052	1	U.S.	Amiodarone, warfarin, BP meds, antabuse, NSAID	Renal cell carcinoma, hemorrhaged 2 weeks post nephrectomy on warfarin and amiodarone
6026	0034	69	M	Abdominal pain	595	15	South America	BP med	Diagnosis liver cancer per son. No hospital records available
5002	0367	71	M	Duodenal ulcer	816	Unknown		Ramipril, paracetamol, immucyst, bisoprolol, atorvastatin, PPI, furosemide	Miscoded, subject did not die
7776	0042	87	M	Inguinal hernia	72	1	Colombia	pressors	Bowel perforation during inguinal herniorrhaphy
4145	0037	57	M	Intestinal obstruction	611	1	Canada		Diagnosis of gastric cancer
5482	0269	59	M	Esophageal hemorrhage	212	3	Poland	Aldactone, H2 blocker, PPI, bile therapy, vasopressin, B vitamin	Alcoholic cirrhosis, recurrent esophageal bleed
8617	0009	77	M	Gastrointestinal hemorrhage	303	1	Bulgaria	Acenocoumarin, propaphenone, digoxin, verapamil, cox-2 inhibitor	Study med stopped 66 days prior to death following spinal fracture. On Cox-2 inhibitor and acenocoumarin
1130	0006	68	M	Esophageal rupture	269	1	U.S.	PPI, iron, antacids	Longstanding GERD, died at home, family reports autopsy showed esophageal rupture

Center	Subject ID	Age	Sex	Preferred term	Days on treatment	Days between AE onset and death	Country	Medications	Comments
1280	0011	70	F	Gastroesophageal reflux disease	489	unknown	U.S.	Xanax, inhalers, bisphosphonate, zyprexa, effexor, PPI, cymbalta, torazepam	Miscoded, subject died from subdural hematoma sustained after fall
Placebo-treatment group									
7754	0020	58	M	Peritonitis	293	14	Colombia	BP med, prazocin, antibiotic, beclomethasone	Post operative complication following gastric bypass surgery
Source: Applicant's Table 11.3.3.2.1 Pg 5622 JUPITER CSR; FDA email request: 18 August 2009, Table 2									

An additional rosuvastatin-treated subject had a non-treatment emergent gastrointestinal AE of abdominal pain leading to death. Subject 8005-0019, a 70-year-old man experienced abdominal pain starting 40 days before randomization. Pancreatic carcinoma was diagnosed on day 267; study medication was stopped on Day 281 and patient died on Day 527.

In the two-year, placebo-controlled study of rosuvastatin, METEOR, there were no deaths attributed to gastrointesintal disorders in either the rosuvastatin group (n=700) or the placebo group (n=281). In the five-year, placebo-controlled trial, CORONA, five (0.2%) deaths and 22 (0.9%) deaths in the rosuvastatin and placebo treatment groups, respectively were attributed to a gastrointestinal cause.

Non-fatal serious adverse events

During the randomized treatment phase, the rosuvastatin treatment group reported 1269/8901 (14.3%) treatment-emergent non-fatal clinical SAEs versus 1269/8901 (14.3%) reported for the placebo group. Table 27 summarizes the treatment-emergent non-fatal clinical SAEs by SOC. Clinical events occurring between 31 March 2008 and each subject's final visit were reported as SAEs.

Table 27: JUPITER: Non-fatal treatment-emergent SAEs (ITT population)

System organ class	Rosuva 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Any non-fatal SAE	**1269 (14.3)**	**1269 (14.3)**
Neoplasms benign, malignant, and unspecified (includes cysts and polyps)	258 (2.9)	261 (2.9)
Infections and infestations	200 (2.2)	220 (2.5)
Gastrointestinal disorders	184 (2.1)	171 (1.9)
Injury, poisoning, and procedural complications	161 (1.8)	142 (1.6)
Musculoskeletal and connective tissue disorders	154 (1.7)	140 (1.6)
Cardiac disorders	152 (1.7)	175 (2.0)
Respiratory, thoracic, and mediastinal disorders	101 (1.1)	108 (1.2)
Nervous system disorders	86 (1.0)	89 (1.0)
Hepatobiliary disorders	57 (0.6)	60 (0.7)
General disorders and administration site conditions	56 (0.6)	61 (0.7)
Renal and urinary disorders	56 (0.6)	75 (0.8)

System organ class	Rosuva 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Vascular disorders	44 (0.5)	69 (0.8)
Reproductive system and breast disorders	43 (0.5)	41 (0.5)
Metabolism and nutrition disorders	33 (0.4)	37 (0.4)
Blood and lymphatic system disorders	26 (0.3)	33 (0.4)
Psychiatric disorders	26 (0.3)	15 (0.2)
Eye disorders	14 (0.2)	20 (0.2)
Skin and subcutaneous tissue disorders	13 (0.1)	12 (0.1)
Endocrine disorders	12 (0.1)	7 (0.1)
Investigations	10 (0.1)	8 (0.1)
Ear and labyrinth disorders	8 (0.1)	11 (0.1)
Immune system disorders	7 (0.1)	2 (<0.1)
Congenital, familial, and genetic disorders	4 (<0.1)	3 (<0.1)
Surgical and medical procedures	3 (<0.1)	1 (<0.1)
Source: Applicant's Table 11.3.4.1.2.2, Pg 8356 CSR JUPITER		

There is a slight imbalance in the gastrointestinal disorders SOC for non-fatal SAEs (rosuvastatin 184/8901, 2.1%; placebo, 171/8901, 1.9%). When looking at the preferred terms for the GI SOC there does not appear to be a pattern of increased occurrence in a particular area of the GI system. The table below lists the non-fatal GI treatment emergent SAEs by preferred terms that occurred in the rosuvastatin group. Preferred terms that occurred in the placebo group but not in the rosuvastatin group were omitted.

Table 28: Non-fatal GI treatment emergent SAE by preferred terms occurring in rosuvastatin treatment group

System organ class	Preferred Term	Rosuvastatin 20 mg N=8901 n(%)	Placebo N=8901 n(%)
Gastrointestinal disorders		184 (2.1)	171 (1.9)
	Gastrointestinal hemorrhage	20 (0.2)	18 (0.2)
	Inguinal hernia	20 (0.2)	18 (0.2)
	Intestinal obstruction	12 (0.1)	9 (0.1)
	Abdominal pain	8 (0.1)	7 (0.1)
	Acute pancreatitis	8 (0.1)	6 (0.1)
	Umbilical hernia	8 (0.1)	6 (0.1)
	Diverticulum	6 (0.1)	4 (<0.1)
	Diarrhea	5 (0.1)	9 (0.1)
	Hiatus hernia	5 (0.1)	2 (<0.1)
	Pancreatitis	5 (0.1)	9 (0.1)
	Small intestinal obstruction	5 (0.1)	8 (0.1)
	Abdominal hernia	4 (<0.1)	1 (<0.1)
	Abdominal pain upper	4 (<0.1)	6 (0.1)
	Colonic polyp	4 (<0.1)	4 (<0.1)
	Crohn's disease	4 (<0.1)	1 (<0.1)
	Gastritis	4 (<0.1)	4 (<0.1)
	Duodenal ulcer hemorrhage	3 (<0.1)	0
	Gastric ulcer hemorrhage	3 (<0.1)	2 (<0.1)
	Hemorrhoids	3 (<0.1)	2 (<0.1)
	Peritonitis	3 (<0.1)	3 (<0.1)
	Rectal prolapse	3 (<0.1)	0

System organ class	Preferred Term	Rosuvastatin 20 mg N=8901 n(%)	Placebo N=8901 n(%)
	Colitis ischemic	2 (<0.1)	2 (<0.1)
	Colitis ulcerative	2 (<0.1)	5 (0.1)
	Diverticulum intestinal	2 (<0.1)	0
	Enterovesical fistula	2 (<0.1)	1 (<0.1)
	Erosive esophagitis	2 (<0.1)	1 (<0.1)
	Gastric ulcer	2 (<0.1)	6 (0.1)
	Gastritis erosive	2 (<0.1)	0
	Gastroesophageal reflux disease	2 (<0.1)	4 (<0.1)
	Ileus	2 (<0.1)	2 (<0.1)
	Ileus paralytic	2 (<0.1)	0
	Irritable bowel syndrome	2 (<0.1)	1 (<0.1)
	Large intestine perforation	2 (<0.1)	0
	Peptic ulcer	2 (<0.1)	2 (<0.1)
	Rectal hemorrhage	2 (<0.1)	4 (<0.1)
	Rectal polyp	2 (<0.1)	0
	Salivary gland cyst	2 (<0.1)	0
	Vomiting	2 (<0.1)	2 (<0.1)
	Abdominal distension	1 (<0.1)	0
	Abdominal strangulated hernia	1 (<0.1)	0
	Abdominal wall hematoma	1 (<0.1)	0
	Ascites	1 (<0.1)	0
	Barrett's esophagus	1 (<0.1)	1 (<0.1)
	Colonic stenosis	1 (<0.1)	1 (<0.1)
	Constipation	1 (<0.1)	1 (<0.1)
	Duodenal ulcer	1 (<0.1)	2 (<0.1)
	Duodenitis	1 (<0.1)	1 (<0.1)
	Enterocele	1 (<0.1)	0
	Food poisoning	1 (<0.1)	0
	Gastric perforation	1 (<0.1)	0
	Gastric polyps	1 (<0.1)	0
	Gastric ulcer perforation	1 (<0.1)	0
	Gastrointestinal pain	1 (<0.1)	0
	Hematemesis	1 (<0.1)	2 (<0.1)
	Hemorrhoidal hemorrhage	1 (<0.1)	0
	Inguinal hernia, obstructive	1 (<0.1)	0
	Intra-abdominal hemorrhage	1 (<0.1)	0
	Large intestinal hemorrhage	1 (<0.1)	0
	Nausea	1 (<0.1)	2 (<0.1)
	Esophagitis	1 (<0.1)	1 (<0.1)
	Esophagitis hemorrhagic	1 (<0.1)	0
	Esophagitis ulcerative	1 (<0.1)	0
	Peptic ulcer hemorrhage	1 (<0.1)	1 (<0.1)
	Peritoneal disorder	1 (<0.1)	0
	Salivary gland calculus	1 (<0.1)	0
	Small intestinal hemorrhage	1 (<0.1)	1 (<0.1)
	Spigelian hernia	1 (<0.1)	0
	Swollen tongue	1 (<0.1)	0
	Volvulus of small bowel	1 (<0.1)	0

Source: Applicant's Table 11.3.4.1.2.2, Pg 8356, CSR JUPITER

The imbalance noted for the psychiatric non-fatal SAEs was attributed to the preferred terms of depression and confusional state. The following table lists the preferred terms in the psychiatric disorder SOC for non-fatal SAEs.

Table 29: Non-fatal Psychiatric SAEs by preferred term

System organ class	Preferred Term	Rosuvastatin 20 mg N=8901 n(%)	Placebo N=8901 n(%)
Psychiatric disorders	Any adverse event	26 (0.3)	15 (0.2)
	Depression	8 (0.1)	4 (<0.1)
	Confusional state	7 (0.1)	1 (<0.1)
	Anxiety	2 (<0.1)	2 (<0.1)
	Delirium	2 (<0.1)	1 (<0.1)
	Insomnia	2 (<0.1)	0
	Major depression	2 (<0.1)	0
	Suicidal ideation	2 (<0.1)	0
	Mental status changes	1 (<0.1)	2 (<0.1)
	Suicide attempt	1 (<0.1)	0
	Acute psychosis	0	1 (<0.1)
	Aggression	0	1 (<0.1)
	Alcohol abuse	0	1 (<0.1)
	Alcoholism	0	2 (<0.1)
	Panic attack	0	1 (<0.1)
	Psychotic disorder	0	1 (<0.1)

Source: Applicant's Table 11.3.4.1.2.2, Pg 8356, CSR JUPITER

Study medication discontinuations and study withdrawals

One secondary endpoint was time to discontinuation of blinded study medication due to adverse events. A distinction was made in JUPITER regarding discontinuations of study medication due to an AE versus an AE leading to study withdrawal or a DAE. Subjects who discontinued study medication did not necessarily withdraw from the study. A similar number of subjects discontinued study medication due to an AE; 495 (5.6%) in the rosuvastatin group, and 486 (5.5%) in the placebo group. There was no statistically significant difference in time to discontinuation of study medication due to an AE between the treatment groups. The reasons for discontinuing study medication are summarized in the table below. Twice as many placebo-treated subjects discontinued study medication due to a clinical event and three times as many subjects in the placebo group discontinued study treatment to initiate open-label statin treatment.

Table 30: JUPITER: Reasons for discontinuing study medication (ITT population)[a]

Reason	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Clinical event	72 (0.8)	153 (1.7)
Initiation of open label statin therapy	51 (0.6)	157 (1.8)
Adverse event	584 (6.6)	553 (6.2)
Other	1002 (11.3)	1048 (11.8)
Not specified	2 (<0.1)	12 (0.1)
Total	1711 (19.2)	1923 (21.6)

a Subjects may appear in more than one reason category

Reason	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Source: Applicant's Table 11.1.1.8.2.4.1, Pg 1865 CSR JUPITER		

In JUPITER, 1.6% (143/8901) of rosuvastatin-treated subjects versus 1.8% (158/8901) of placebo-treated subjects experienced an AE that led to study withdrawal. The DAEs that led to study withdrawal are summarized in the following table.

Table 31: JUPITER: Number and frequency of subjects with treatment-emergent adverse events leading to study withdrawal (ITT population)

System organ class	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Any DAE	**143 (1.6)**	**158 (1.8)**
Musculoskeletal disorders	37 (0.4)	31 (0.3)
Gastrointestinal disorders	22 (0.2)	11 (0.1)
Neoplasms benign, malignant, and unspecified (includes cysts and polyps)	22 (0.2)	24 (0.3)
General disorders and administration site conditions	14 (0.2)	21 (0.2)
Nervous system disorders	8 (0.1)	18 (0.2)
Infections and infestations	7 (0.1)	3 (<0.1)
Injury, poisoning, and procedural complications	6 (0.1)	1 (<0.1)
Cardiac disorders	5 (0.1)	10 (0.1)
Skin and subcutaneous tissue disorders	5 (0.1)	5 (0.1)
Investigations	4 (<0.1)	4 (<0.1)
Vascular disorders	4 (<0.1)	5 (0.1)
Hepatobiliary disorders	3 (<0.1)	4 (<0.1)
Psychiatric disorders	3 (<0.1)	2 (<0.1)
Reproductive system and breast disorders	3 (<0.1)	0
Respiratory, thoracic, and mediastinal disorders	3 (<0.1)	9 (0.1)
Metabolism and nutrition disorders	2 (<0.1)	9 (0.1)
Renal and urinary disorders	1 (<0.1)	3 (<0.1)
Blood and lymphatic system disorders	0	1 (<0.1)
Source: Applicant's Table 36, Pg 89 CSR JUPITER		

Musculoskeletal disorders were the most common reason for study withdrawal in both treatment groups. Myalgia was the preferred term listed most frequently in the rosuvastatin treatment group (25/8901, 0.3%) and placebo treatment group (15/8901, 0.2%) as reason for withdrawal (Applicant's Table 11.3.5.1.2.2, Pg 26172 CSR JUPITER). There was a slightly higher number of DAEs due to gastrointestinal disorders in the rosuvastatin group. Of these the most common treatment-emergent AE was abdominal pain (3 rosuvastatin subjects, 2 placebo subjects) in both groups.

Significant adverse events

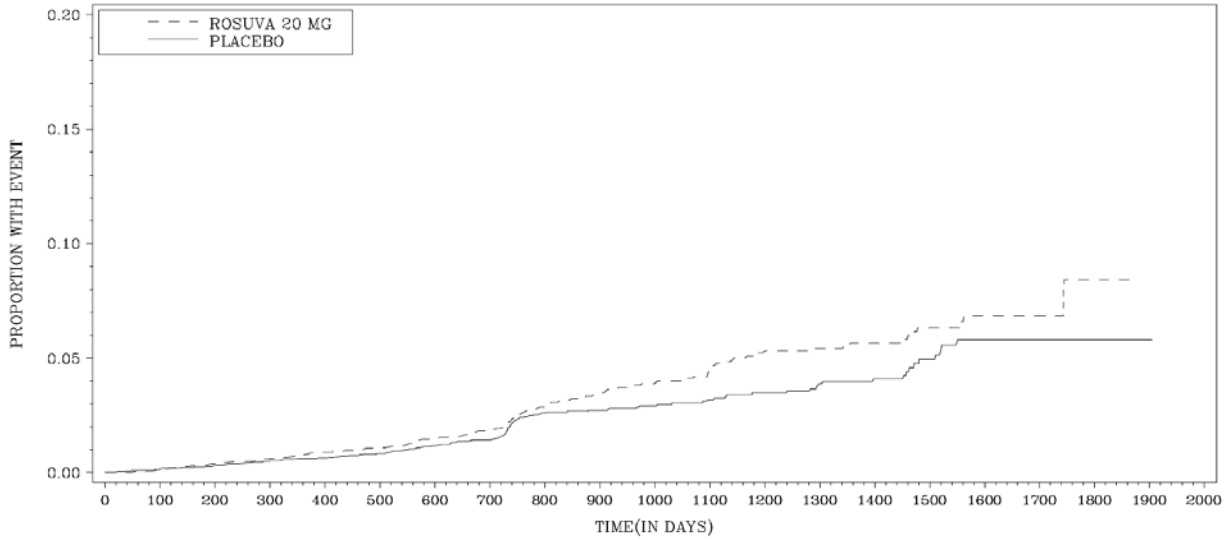
Metabolic adverse events: Investigator-reported diabetes mellitus

A pre-specified secondary endpoint was time to investigator-reported diabetes which was assessed for every 3 months. In JUPITER, there was a higher frequency of rosuvastatin-treated subjects reported with diabetes as compared to the placebo-treated subjects (Table 32, Figure 8).

Table 32: JUPITER: Summary and time to development of (investigator-reported) diabetes mellitus (without 30 March 2008 cutoff)

	Number of events (% of subjects having an event)						
	Rosuvastatin 20 mg N=8901		Placebo N=8901				
	n	%	n	%	HR	95% CI	p-value
Investigator reported diabetes	251	2.8	205	2.3	1.27	1.05, 1.53	0.015
Source: Applicant's Table 11.3.6.1.2.7 and 11.3.6.1.2.8, Pg 31998 and 31999, CSR							

Figure 8: JUPITER: Kaplan-Meier curve of time to investigator-reported diabetes (without 30 March 2008 cutoff) (ITT population)



Source: Applicant's Figure 11.3.6.1.2.9, Pg 32000, CSR JUPITER

Criteria used to qualify as investigator-reported diabetes were new use of insulin or an oral hypoglycemic agent, a positive glucose tolerance test, a random glucose level over 200 mg/dL with symptoms of diabetes, or repeated fasting glucose levels >126 mg/dL. These events were collected on the case report forms but incident cases were not adjudicated. The following table summarizes the criteria met by JUPITER subjects for investigator-reported diabetes.

Table 33: JUPITER: Summary of criteria for investigator-reported diabetes (without 30 Mar 2008 cutoff) (ITT population)

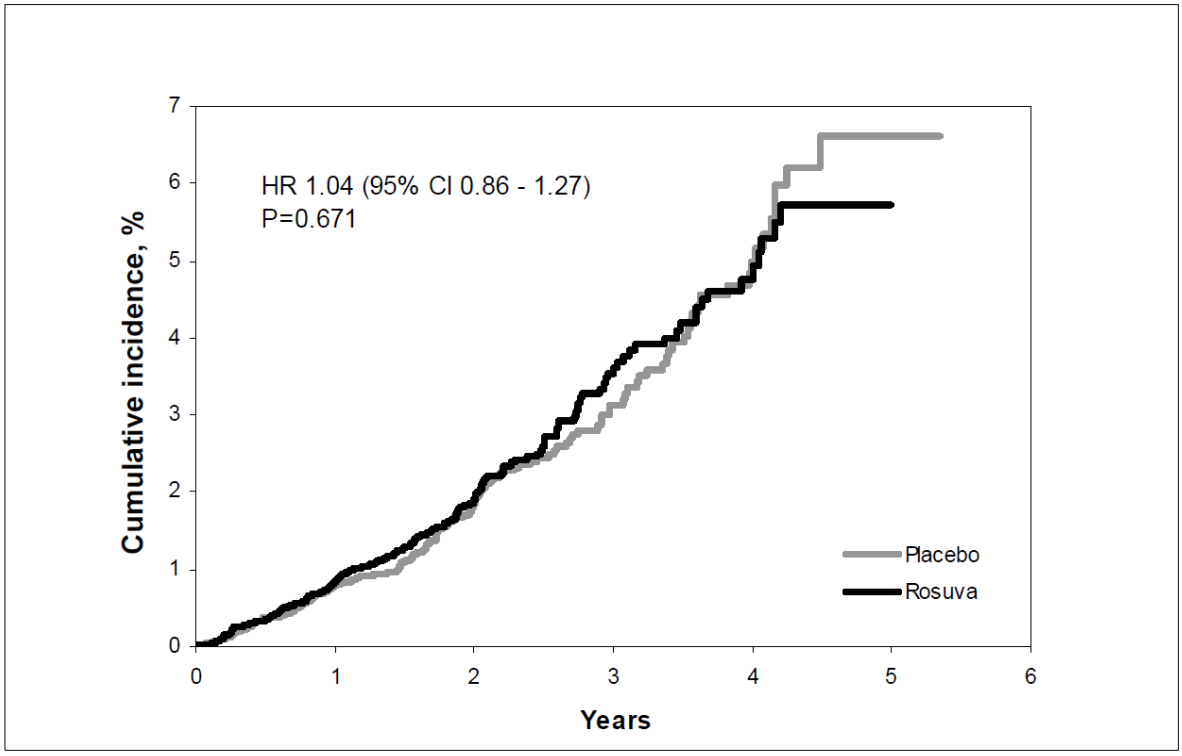
Reason given for diabetes reported[a]	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)	Total N=17802 n (%)
Total incident cases of diabetes	251 (2.8)	205 (2.3)	456 (2.6)
New use of insulin	8 (3.2)	5 (2.4)	13 (2.9)
New use of oral hypoglycemic agent	122 (48.6)	106 (51.7)	228 (50.0)
Positive glucose tolerance test (>200 mg/dL)	55 (21.9)	38 (18.5)	93 (20.4)
Repeated fasting glucose >126 mg/dL	151 (60.2)	130 (63.4)	281 (61.6)
Random blood sugar ≥ 200 mg/dL	28 (11.2)	19 (9.3)	47 (10.3)
Other[b]	13 (5.2)	8 (3.9)	21 (4.6)
[a] More than one reason per person included in table			

Reason given for diabetes reported[a]	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)	Total N=17802 n (%)

[b] Diagnosis made with criteria that was unspecified or different from listed reasons
Source: Table 11.3.6.1.2.12, Pg 32003, CSR

An analysis of time to first use of diabetic medication was performed including subjects with or without investigator-reported diabetes. There was no statistically significant difference between rosuvastatin and placebo treatment groups (Figure 9). It should be noted that use of anti-diabetic medication was only one criterion for the diagnosis of diabetes.

Figure 9: Kaplan-Meier plot of time to use of diabetic medication



Source: Applicant's Figure 1, IR response 01 September 2009, Pg 6

In a post-hoc analysis, the Applicant evaluated the baseline characteristics of the JUPITER cohort who developed investigator-reported diabetes versus those who did not. As expected subjects who developed investigator-reported diabetes were more likely to have a diagnosis of impaired fasting glucose, metabolic syndrome, and be overweight at baseline. However, overall, the JUPITER treatment groups were balanced at baseline with regard to metabolic syndrome, fasting glucose, and BMI.

Table 34: JUPITER: Baseline characteristics of subjects with and without investigator-reported diabetes

	Diabetes		No diabetes	
	Rosuvastatin 20 mg	**Placebo**	**Rosuvastatin 20 mg**	**Placebo**
N	251	205	8650	8696
FSG ≥100 mg/dL, %	76.5	76.1	29.6	30.6
FSG (mean), mg/dL	107.3	108.8	94.3	94.6
BMI ≥25 kg/m^2, %	92.4	91.7	76.3	76.6
BMI (mean), kg/m^2	32.66	32.41	28.96	29.92
Weight (kg)	93.49	92.94	81.72	81.74
TG ≥150 mg/dL, %	57.0	51.7	31.9	32.5
Metabolic syndrome, %	77.7	79.0	40.0	41.0
Source: Applicant's Table 40, Pg 97, Table 11.3.8.1.13-14, Pg 79456-7, Table 11.3.8.1.9, Pg 79452-3 JUPITER CSR				

The Applicant reported that in the group with impaired fasting glucose (≥100 mg/dL) at baseline there was significant reduction in the number and time to MCE (Table 35). There was also no significant treatment interaction based on baseline FSG below or above 100 mg/dL.

Table 35: JUPITER: Prespecified subgroup analysis of number of MCE in subjects with impaired fasting glucose at baseline (ITT population)

	Number of events				
	Rosuva 20 mg N=8901	**Placebo N=8901**			
	n	**n**	**HR**	**95% CI**	**p-value**
< 100 mg/dL	87	167	0.52	0.40, 0.67	0.257
≥ 100 mg/dL	55	84	0.66	0.47, 0.93	
Source: Applicant's Table 12.1.9.1.4.1, Pg 699, Appendix 12.1.9					

The Applicant reported that no trends in clinical or laboratory findings related to diabetes were identified beyond what is listed above, except that subjects in the rosuvastatin treatment group had a slightly greater weight gain during the period of follow-up compared to subjects in the placebo group (mean change 0.44 kg rosuvastatin vs. 0.15 kg placebo); however, when evaluated by who developed diabetes and who did not this trend was not observed. Both the rosuvastatin- and placebo-treated subjects who developed diabetes had less weight gain compared to baseline than subjects who did not develop diabetes.

Table 36: JUPITER: Change in weight from baseline in those with and without development of diabetes

	Diabetes		No diabetes	
	Rosuvastatin 20 mg	**Placebo**	**Rosuvastatin 20 mg**	**Placebo**
Change in weight from baseline (kg)	0.10	-0.96	0.45	0.18
Source: Applicant's Table 40, Pg 97, Table 11.3.8.1.13-14, Pg 79456-7, CSR				

Fasting blood glucose and HbA1c values were assessed at baseline, Year 2, then annually, and at the final visit. There were no differences in fasting glucose levels between the two treatment groups. Overall there was a trend of increasing fasting glucose levels (increase of 3% mean change from baseline) in both groups. HbA1c levels rose in both groups, with the rosuvastatin group experiencing a greater increase compared to the placebo group. At the final visit there was a significantly different change from baseline of 0.08% points between the two treatment groups.

Table 37: JUPITER: Fasting glucose and HbA1c levels at baseline and during follow-up (ITT population)

	Rosuvastatin 20 mg		Placebo		
	N	Mean value (SD)	N	Mean value (SD)	p-value[a]
Fasting glucose, mg/dL					
Baseline	8875	95 (11.5)	8878	95 (11.8)	0.134
Year 2	3520	100 (17.9)	3502	100 (18.0)	0.344
Year 3	1198	100 (19.3)	1140	99 (15.9)	0.137
Year 4	440	99 (15.3)	414	98 (15.5)	0.147
Final	7124	98 (19.7)	7002	98 (18.9)	0.442
Change in fasting glucose, mg/dL					
Baseline to Year 2	3515	5 (16.0)	3499	4 (16.2)	0.057
Baseline to Year 3	1197	4 (17.0)	1140	3 (14.2)	0.097
Baseline to Year 4	440	2 (13.1)	414	2 (14.1)	0.423
Baseline to Final	7104	3 (18.3)	6985	3 (17.6)	0.078
HbA1c, %					
Baseline	8856	5.7 (0.42)	8853	5.7 (0.45)	0.0014
Year 2	3514	5.9 (0.48)	3497	5.8 (0.47)	<0.0001
Year 3	1195	5.9 (0.46)	1134	5.8 (0.42)	<0.0001
Year 4	439	5.9 (0.49)	409	5.9 (0.43)	0.038
Final	7136	6.0 (0.50)	7054	6.0 (0.49)	<0.0001
Change in HbA1c, %					
Baseline to Year 2	3506	0.29 (0.34)	3480	0.19 (0.33)	<0.0001
Baseline to Year 3	1191	0.29 (0.33)	1131	0.19 (0.29)	<0.0001
Baseline to Year 4	438	0.31 (0.34)	406	0.21 (0.33)	<0.0001
Baseline to Final	7115	0.30 (0.35)	7013	0.22 (0.40)	<0.0001

[a] p-values for treatment group difference determined by t-test for glucose and HbA1c
Source: Applicant's Table 41-42, Pg 98-99, CSR

Reviewer comment: As noted above, neither HbA1c nor a one-time occurrence of a fasting glucose >126 mg/dL was considered a criterion for investigator-reported diabetes. The Applicant submitted tables summarizing subjects developing diabetes by treatment and visit using the criteria of HbA1c >6.5%, the occurrence of fasting glucose >126 mg/dL at any time in the study, and either HbA1c >6.5% or fasting glucose >126 mg/dL. As shown below there is an imbalance which demonstrates a higher incidence in the rosuvastatin-treated group of developing diabetes using HbA1c, fasting glucose levels, or either value. These numbers are also higher than the 251 rosuvastatin and 205 placebo cases of investigator-reported diabetes. The American Diabetes Association does not use HbA1c as a criterion for the diagnosis of diabetes.

Table 38: JUPITER: Subjects developing diabetes using HbA1c >6.5% (ITT population)

	Rosuvastatin 20 mg		Placebo		p-value[a]
	N	n (%)	N	n (%)	
Month 24	3474	326 (9.4)	3454	227 (6.6)	<0.001
Month 36	1184	113 (9.5)	1122	57 (5.1)	<0.001
Month 48	431	45 (10.4)	401	24 (6.0)	0.020
Final	7132	900 (12.6)	7054	653 (9.3)	<0.001

[a] Chi-square test comparing the distribution between treatments
Source: Table 11.3.6.1.2.4, Pg 31995 CSR

Table 39: JUPITER: Subjects developing diabetes using FSG ≥ 126 mg/dL at least once (ITT population)

	Rosuvastatin 20 mg		Placebo		p-value[a]
	N	n (%)	N	n (%)	
Month 24	3486	180 (5.2)	3461	178 (5.1)	0.969
Month 36	1188	82 (6.9)	1129	58 (5.1)	0.075
Month 48	432	25 (5.8)	407	21 (5.2)	0.690
Final	7120	422 (5.9)	7000	374 (5.3)	0.151

[a] Chi-square test comparing the distribution between treatments
Source: Table 11.3.6.1.2.5, Pg 31996 CSR

Table 40: JUPITER: Subjects developing diabetes using HbA1c >6.5% or FSG ≥ 126 mg/dL at least once (ITT population)

	Rosuvastatin 20 mg		Placebo		p-value[a]
	N	n (%)	N	n (%)	
Month 24	3500	405 (11.6)	3481	331 (9.5)	<0.001
Month 36	1192	152 (12.8)	1132	93 (8.2)	<0.001
Month 48	433	54 (12.5)	407	32 (7.9)	<0.001
Final	7196	1100 (15.3)	7102	855 (12.0)	<0.001

[a] Chi-square test comparing the distribution between treatments
Source: Table 11.3.6.1.2.6, Pg 31997 CSR

Other data sources regarding diabetes and CRESTOR

The Applicant reported that there was no statistically significant difference in diabetes reported as an AE in two long-term, placebo-controlled studies of rosuvastatin, METEOR and CORONA. The Agency asked for the analysis to support the above statement. The results of this analysis included information from another long-term placebo-controlled trial of patients, AURORA. The trials' databases were searched for diabetes-related adverse events (Appendix E). CORONA and AURORA did not exclude subjects based on the presence of impaired fasting glucose or diabetes mellitus. No fasting plasma glucose or HbA1c levels were obtained during these trials.

Brief description of trials: METEOR, CORONA, AURORA
METEOR was a double-blind, placebo-controlled study of 984 subjects randomized in a 5:2 fashion into 2 parallel treatment arms over a period of 104 weeks. The study was designed to assess the efficacy of rosuvastatin 40 mg in altering the natural history of carotid intima media thickness as compared to placebo. Fasting glucose measurements were obtained at Week -6, Week 0, Week 6, Week 13, and Week 104. Subjects with a history or current diagnosis of diabetes were excluded from this study.

CORONA was a 5-year randomized, placebo-controlled study comparing rosuvastatin 10 mg to placebo in patients with chronic symptomatic heart failure. The ITT population consisted of 5011 (2514 rosuvastatin, 2497 placebo) patients. Subjects were not excluded for diabetes mellitus, or abnormal screening blood glucose or HbA1c levels.

AURORA was a randomized, placebo-controlled study comparing rosuvastatin 10 mg to placebo in patients with end stage renal disease receiving hemodialysis. The ITT population consisted of 2773 (1389 rosuvastatin, 1384 placebo) patients. As with CORONA there were no exclusion criteria based on presence of diabetes mellitus or abnormal glucose or HbA1c levels.

The following table lists the mean fasting glucose levels at baseline and at final visit in the METEOR and JUPITER trials. The mean fasting glucose values are similar at baseline and final visit in both trials. There are no large differences between the treatment and placebo groups in either trial.

Table 41: JUPITER: Fasting glucose levels at baseline and final visit, METEOR and JUPITER trials (Safety and ITT population, respectively)

	METEOR		**JUPITER**	
Fasting glucose, mg/dL	**Rosuvastatin 40 mg N=700**	**Placebo N=281**	**Rosuvastatin 20 mg N=8901**	**Placebo N=8901**
Baseline (Week 0)	**N=640**	**N=254**	**N=8875**	**N=8878**
Mean	95	97	95	95
Standard deviation	12.2	14.4	11.5	11.8
Min	61	67	40	39
Max	211	236	175	223
Final	**N=520**	**N=207**	**N=7124**	**N=7002**
Mean	99	99	98	98
Standard deviation	14.9	14.9	19.7	18.9
Min	67	74	14	12
Max	220	202	552	401
Applicant's Table 11.3.7.1.3.1, Pg 71656, JUPITER CSR, Table 1, Pg 5 IR response 21 August 2009				

The following table includes the number, frequency, and statistical significance of any diabetes-related adverse events occurring during the METEOR, CORONA, AURORA, and JUPITER trials.

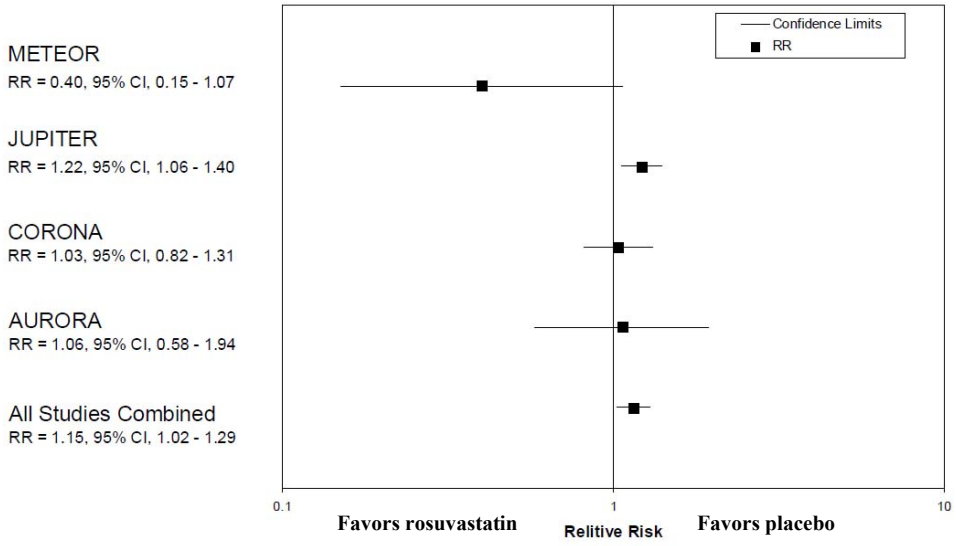
Table 42: Number and frequencies of treatment-emergent diabetes-related adverse events during the treatment phase in METEOR, CORONA, AURORA, and JUPITER trials

	METEOR p-value[a] = 0.0431		CORONA (randomized pop) p-value = 0.6437		AURORA (randomized pop) p-value = 0.9006		JUPITER (randomized pop) p-value = 0.002	
MedDRA preferred term	**Rosuva 40 mg N=701 n (%)**	**Placebo N=282 n (%)**	**Rosuva 10 mg N=2416 n (%)**	**Placebo N=2405 n (%)**	**Rosuva 10 mg N=1003 n (%)**	**Placebo N=1042 n (%)**	**Rosuva 20 mg N=8901 n (%)**	**Placebo N=8901 n (%)**
Any diabetic AE	**8 (1.1)**	**8 (2.8)**	**139 (5.8)**	**131 (5.4)**	**21 (2.1)**	**21 (2.0)**	**448 (5.0)**	**361 (4.1)**
Diabetes mellitus	1 (0.1)	4 (1.4)	84 (3.5)	82 (3.4)	6 (0.6)	11 (1.1)	237 (2.7)	186 (2.1)
Blood glucose increased	5 (0.7)	1 (0.4)	12 (0.5)	14 (0.6)	0	2 (0.2)	82 (0.9)	50 (0.6)
Glucose tolerance impaired	0	0	5 (0.2)	2 (0.1)	2 (0.2)	1 (0.1)	41 (0.5)	42 (0.5)
Glycosylated hemoglobin increased	0	0	0	2 (0.1)	0	0	41 (0.5)	21 (0.2)
Hyperglycemia	1 (0.1)	0	21 (0.9)	19 (0.8)	8 (0.8)	2 (0.2)	28 (0.3)	28 (0.3)
Glycosuria	0	0	0	0	0	0	27 (0.3)	32 (0.4)
Impaired fasting glucose	0	0	0	0	0	0	13 (0.1)	21 (0.2)
Blood glucose abnormal	0	0	1 (<0.1)	1 (<0.1)	0	0	4 (<0.1)	4 (<0.1)
Polyuria	0	1 (0.4)	2 (0.1)	0	0	0	4 (<0.1)	3 (<0.1)
Ketonuria	0	1 (0.4)	0	0	0	0	3 (<0.1)	5 (0.1)
Metabolic syndrome	0	0	1 (<0.1)	0	0	0	3 (<0.1)	4 (<0.1)
Thirst	1 (0.1)	0	1 (<0.1)	1 (<0.1)	2 (0.2)	1 (0.1)	3 (<0.1)	2 (<0.1)
Glucose tolerance test abnormal	0	0	0	0	0	0	1 (<0.1)	0
Insulin resistance	0	0	0	0	0	0	1 (<0.1)	1 (<0.1)
Polydipsia	0	1 (0.4)	1 (<0.1)	0	0	0	0	2 (<0.1)
Diabetes mellitus inadequate control	0	0	19 (0.8)	18 (0.7)	0	1 (0.1)	0	0
Diabetic ketoacidosis	0	0	1 (<0.1)	0	0	1 (0.1)	0	0
Hyperglycemic hyperosmolar nonketotic	0	0	1 (<0.1)	0	0	0	0	0
Glucose urine present	0	0	0	1 (<0.1)	0	0	0	0
Type 2 diabetes mellitus	0	0	0	0	4 (0.4)	4 (0.4)	0	0

[a] p-value calculated by chi-square test
Source: Applicant's Tables 2, 3, 4 Pg 5-7 IR response 21 August 2009 and 10 September 2009

The data on diabetic-related AEs were combined from the 4 trials to estimate relative risk and the 95% confidence interval using a Mantel-Haenszel approach. From this plot the RR is 1.15 (95% CI 1.02, 1.29) suggesting there is a small difference in diabetes-related AEs in rosuvastatin-exposed subjects versus unexposed subjects.

Figure 10: Forest plot of METEOR, CORONA, AURORA, and JUPITER diabetes-related AE data

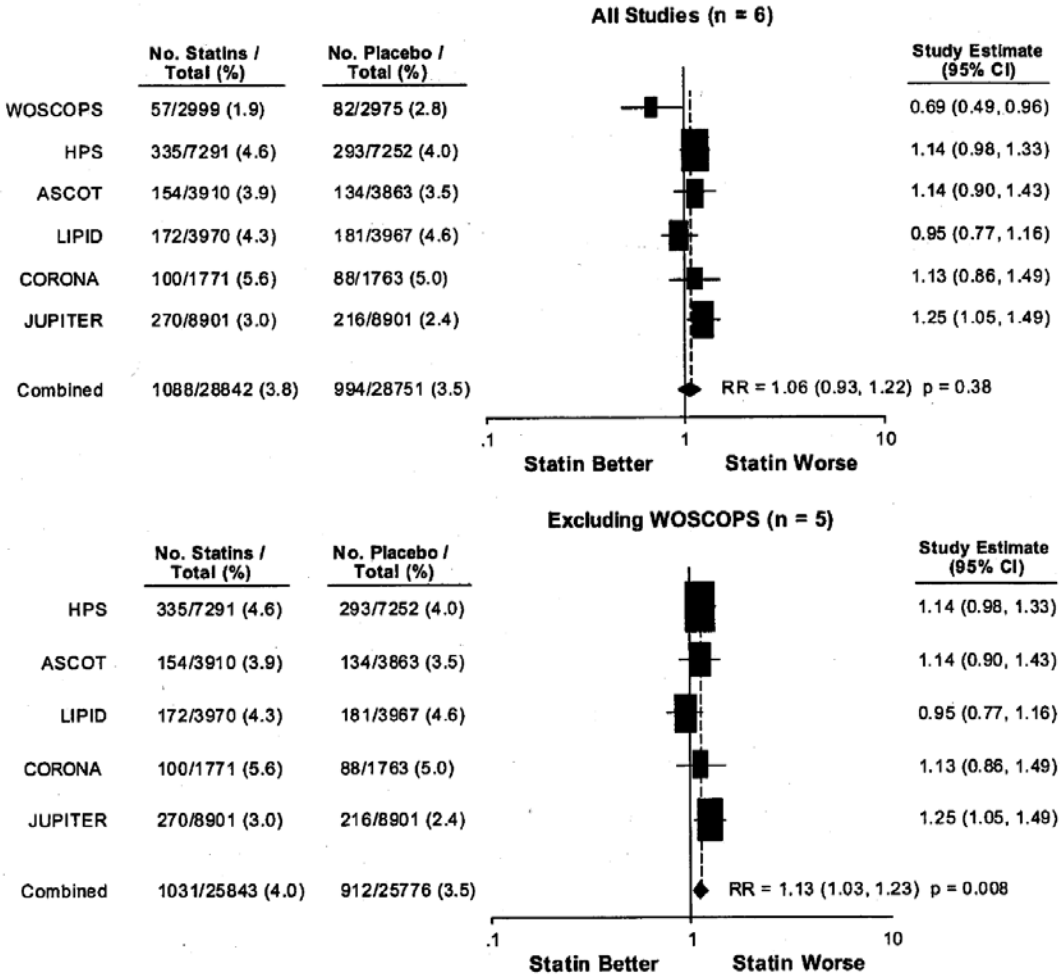


Source: IR request 10 September 2009, Figure 1, Pg 8

A recent meta-analysis evaluated the effect of statin therapy on incident diabetes.[31] The resulting analysis of five randomized, placebo-controlled trials (JUPITER included) eligible due to reporting of incident diabetes during follow-up demonstrated a relative risk of developing diabetes of 1.13 (95% CI 1.03, 1.23; p=0.008) (Figure 11). However, when the WOSCOPS trial which had demonstrated a protective effect against diabetes was included the relative risk was 1.06 (95% CI 0.93, 1.23; p=0.38) but this analysis exhibited significant heterogeneity. This meta-analysis was limited in that few statin trials have data available on diabetes incidence, the diagnostic criteria for diabetes were not uniform, and WOSCOPS data were limited to men.

[31] Rajpathak et al. Statin therapy and risk of developing type 2 diabetes: a meta-analysis. Diabetes Care 2009; 32:1924-29.

Figure 11: Meta-analysis of statin therapy and diabetes risk



Source: Rajpathak et al. Diabetes Care 2009; 32: 1924-1929

Reviewer comment: Based on the available clinical evidence it appears that as a drug class statins increase the incidence of diabetes mellitus, although there have been no prospective clinical trials with an adjudicated pre-defined endpoint of diabetes incidence examining the relationship between statin use and diabetes incidence or its effect on microvascular disease and its complications. It is well established that people with diabetes are at high risk for major cardiovascular events and are more likely to die due to a cardiovascular event. Large clinical trials have demonstrated that with and without clinically evident cardiovascular disease statins provide a significant treatment benefit in people with diabetes.[32,33] *In JUPITER, 31% of study subjects were diagnosed with impaired fasting glucose at baseline and within this subgroup a treatment benefit was observed [HR 0.66 (95% CI 0.47, 0.93)]. However, the JUPITER trial was relatively*

[32] Collins et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trail. Lancet 2003;361:2005-16.
[33] Calhoun et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicenter randomized placebo-controlled trial. Lancet 2004; 364:685-96.

short in duration (median 1.9 years) and therefore the long-term complications are unknown. At this time, it is this clinical reviewer's opinion that the treatment benefit observed in the JUPITER trial outweigh the risk, but further clinical trials are needed to further define this benefit/risk ratio.

Hepatic adverse events

In JUPITER a total of 216 (2.4%) rosuvastatin-treated subjects and 186 (2.1%) placebo-treated subjects experienced a hepatic-related adverse event. The most common AE was related to abnormal laboratory levels and occurred with higher frequency in the rosuvastatin-treatment group. The following table lists any hepatic-related AE that occurred in the randomized treatment phase (not just treatment-emergent AEs). There were two cases of chronic hepatic failure in rosuvastatin-treated patients and two cases of hepatic failure in placebo-treated patients.

Table 43: Number and percentage of subjects with hepatic-related adverse events reported during the randomized treatment phase, by SOC and preferred term (ITT population)[a]

System Organ Class Preferred Term	**Rosuvastatin** **N=8901** **n (%)**	**Placebo** **N=8901** **n (%)**
Any hepatic adverse event	**216 (2.4)**	**186 (2.1)**
Investigations	**165 (1.9)**	**134 (1.5)**
ALT increased	127 (1.4)	93 (1.0)
Hepatic enzyme increased	30 (0.3)	31 (0.3)
AST increased	7 (0.1)	6 (0.1)
GGT increased	7 (0.1)	5 (0.1)
Alkaline phosphatase increased	4 (<0.1)	3 (<0.1)
Liver function test abnormal	2 (<0.1)	2 (<0.1)
Blood bilirubin increased	1 (<0.1)	4 (<0.1)
Blood LDH increased	1 (<0.1)	0
Hepatobiliary disorders	**48 (0.5)**	**53 (0.6)**
Hepatic steatosis	17 (0.2)	22 (0.2)
Hepatic function abnormal	13 (0.1)	6 (0.1)
Hepatomegaly	6 (0.1)	6 (0.1)
Hepatic cirrhosis	3 (<0.1)	4 (<0.1)
Hepatitis	3 (<0.1)	2 (<0.1)
Chronic hepatic failure	2 (<0.1)	0
Jaundice cholestatic	2 (<0.1)	2 (<0.1)
Autoimmune hepatitis	1 (<0.1)	0
Hepatosplenomegaly	1 (<0.1)	0
Jaundice	1 (<0.1)	6 (0.1)
Liver disorder	1 (<0.1)	2 (<0.1)
Alcoholic liver disease	0	1 (<0.1)
Hepatic failure	0	2 (<0.1)
Hepatitis alcoholic	0	2 (<0.1)
Hepatitis cholestatic	0	1 (<0.1)
Hepatitis toxic	0	1 (<0.1)

System Organ Class Preferred Term	Rosuvastatin N=8901 n (%)	Placebo N=8901 n (%)
Infections and infestations	**4 (<0.1)**	**3 (<0.1)**
Hepatitis C	2 (<0.1)	1 (<0.1)
Hepatitis A	1 (<0.1)	1 (<0.1)
Hepatitis B	1 (<0.1)	1 (<0.1)
Gastrointestinal disorders	**3 (<0.1)**	**7 (0.1)**
Ascites	3 (<0.1)	7 (0.1)
Skin and subcutaneous tissue disorders	**1 (<0.1)**	**0**
Yellow skin	1 (<0.1)	0

[a] AE number in this table are all AEs occurring during the randomized treatment period and not just treatment-emergent AEs
Source: Table 11.3.6.1.1.4, Page 31981, CSR

The two chronic hepatic failure AEs in the rosuvastatin treatment group are discussed below:

- Subject 7162-0136: An 82-year-old Hispanic man with a history of chronic obstructive pulmonary disease on theophylline and salbutamol was randomized to rosuvastatin 20 mg on (b) (6) and reported chronic liver failure on Day 226 and withdrew from the study due to this event. Approximately two years later, the subject was still alive and had not experienced any of the primary efficacy endpoints. The labs available do not show an elevation in ALT; on Week -4 the ALT was 11 U/L and on Week 26 (Day 185) the ALT was 16 U/L.

- Subject 1270-0015, a 71-year-old Caucasian man, was randomized to rosuvastatin 20 mg on (b) (6). His past medical history was significant for prostate cancer (1997) and skin cancer (1996). During the study he experienced the adverse events of proteinuria (b) (6)), urinary casts (b) (6)), and hematuria (b) (6)). Concomitant medications at baseline included hydroxyzine for insomnia, and diphenhydramine hydrochloride (Benadryl) for seasonal allergies. He was treated for 5 days with levaquin for a kidney infection on Days 218-223. Available labs showed a normal ALT of 8 U/L at baseline that peaked to 45 U/L on Day 91 and remained elevated. On Day (b) hepatic cirrhosis and chronic hepatic failure was noted. The subject died on Day (b) (6) of pneumonia and septic shock secondary to end-stage liver disease and cirrhosis.

Hepatic biochemistry

Clinically significant laboratory findings related to the hepatic system were defined as an ALT elevation >3x ULN on 2 occasions. Serum AST, bilirubin, and alkaline phosphatase were not routinely monitored in JUPITER; however, at the discretion of the site investigator a bilirubin level could be measured. Evidence for potential severe hepatotoxicity may be signaled by a set of findings called Hy's Law. These findings consist of an increased rate of transaminase elevations, no significant evidence of obstruction, and a rise in bilirubin to 2x ULN in the absence of concurrent hepatic infection or injury. No Hy's law cases were identified in rosuvastatin-treated subjects. Two subjects were identified with bilirubin >2x ULN, AST >3x ULN, and alkaline

phosphatase <2x ULN. One was a placebo-treated subject and the other was a rosuvastatin-treated subject with a concurrent AE of hepatitis C.

- Subject 6018-0025: A 64-year-old Caucasian male with a history of benign prostatic hypertrophy was randomized to placebo and experienced significant elevations in ALT 1338 U/L, AST 606 (ULN 22 mU/mL), bilirubin 2.75 (ULN 1.10 mg/dL), and alkaline phosphatase of 95 (ULN 70 mU/mL), and CK 154 U/L approximately 3 months after randomization. The subject discontinued study medication, but continued participation in follow-up visits. At his final visit, almost 2 years after starting the JUPITER trial, his ALT was slightly elevated at 45 U/L, CK was 112 U/L. He was on no concomitant medications.

- Subject 8488-0022: A 62-year-old Caucasian male with a history of osteopenia, supraventricular tachycardia, and obstructive pulmonary disease was randomized to 20 mg rosuvastatin on (b) (6). He was diagnosed on Day 367 with an elevated ALT (530 U/L), elevated AST (672 U/L), elevated bilirubin 7.86, and alkaline phosphatase of 95 and Hepatitis C. He discontinued study medication on (b) (6) due to this SAE; however, he did not withdraw his participation in the JUPITER trial. Repeat ALT 6 months later demonstrated a reduction to 71 U/L with normal values of ALT one year after diagnosis.

In JUPITER, an ALT >3x ULN on 2 consecutive occasions was defined as "clinically important" and subjects were asked to discontinue the study medication, but were to be followed for the study duration. It was left to the clinical investigator's discretion regarding further work-up.

The following table lists the number and frequency of subjects with significantly elevated ALT and/or AST values.

Table 44: Number (%) of subjects with elevations of ALT in the randomized treatment phase (ITT population)

ALT (U/L)	Rosuvastatin 20 mg N=8624 n (%)	Placebo N=8364 n (%)
AST >3x ULN and/or ALT >3x ULN	124 (1.4)	88 (1.0)
ALT >3x ULN on 2 consecutive occasions	23 (0.3)	17 (0.2)
AST >5x ULN and/or ALT >5x ULN	53 (0.6)	25 (0.3)
AST >10x ULN and/or ALT >10x ULN	12 (0.1)	6 (0.1)
Source: Applicant's Table 43, Pg 101 CSR JUPITER, IR response to 13 October 2009		

The percentage of subjects in the JUPITER trial with an ALT >3x ULN and/or an AST >3x ULN was similar to the percentage observed in a pooled analysis of placebo-controlled trials which demonstrated 1.1% of subjects taking rosuvastatin versus 0.5% of subjects treated with placebo had an elevated ALT according to the current CRESTOR label. In a 2007 analysis funded by the Applicant, safety data from 16,876 patients receiving rosuvastatin 5 to 40 mg observed ≤0.2% occurrence of ALT >3x ULN on 2

consecutive occasions.[34] These numbers are similar to what was observed in the JUPITER trial.

Skeletal muscle adverse events

Muscle-related AEs occurred at a higher incidence in the rosuvastatin-treatment group compared to the placebo group. Myalgia was the most commonly reported preferred term in the rosuvastatin (8.0%) and placebo groups (7.2%). There was one case of rhabdomyolysis in JUPITER in a rosuvastatin-treated subject.

- Subject 1778-001: A 90-year-old man on rosuvastatin pending his final visit developed laboratory-confirmed influenza and lay on the floor at home for at least 24 hours, unable to arise due to weakness. At the hospital, CK was 13,000 and creatinine was 1.5 mg/dL (baseline creatinine 4 years prior was 1.3 mg/dL). Following hydration, he recovered fully; creatinine at final visit was 1.1 mg/dL.

There was nearly twice the number of rosuvastatin-treated subjects with investigator reported elevated CK compared to placebo-treated subjects. The Applicant claims that these events may or may not have met the applicant's criterion for a "clinically important" CK elevation defined as a CK >10x ULN. If the laboratory value was reported by the investigator as abnormal it was considered as an AE of interest; however, it may not have met the predefined definition of a clinically important CK elevation.

Table 45: Number and percentage of subjects with muscle-related adverse events reported during the randomized treatment phase, by SOC and preferred term (ITT population)[a]

System Organ Class Preferred Term	Rosuvastatin N=8901 n(%)	Placebo N=8901 n(%)
Any muscle-related AE	**1421 (16.0)**	**1375 (15.4)**
Investigations	**63 (0.7)**	**38 (0.4)**
Blood creatine phosphokinase increased	61 (0.7)	34 (0.4)
Blood creatine increased	2 (<0.1)	4 (<0.1)
Myoglobin blood increased	1 (<0.1)	0
Musculoskeletal and connective tissue disorders	**1296 (14.6)**	**1225 (13.8)**
Myalgia	714 (8.0)	639 (7.2)
Muscle spasm	333 (3.7)	314 (3.5)
Musculoskeletal pain	295 (3.3)	319 (3.6)
Muscular weakness	84 (0.9)	72 (0.8)
Musculoskeletal discomfort	16 (0.2)	12 (0.1)
Myositis	9 (0.1)	8 (0.1)
Muscle disorder	8 (0.1)	4 (<0.1)
Muscle tightness	8 (0.1)	1 (<0.1)
Muscle fatigue	4 (<0.1)	5 (0.1)

[34] Shepherd et al. Safety of rosuvastatin: update on 16,876 rosuvastatin-treated patients in a multinational clinical trial program. Cardiology 2007;107:433-443.

System Organ Class Preferred Term	**Rosuvastatin N=8901 n(%)**	**Placebo N=8901 n(%)**
Muscle twitching	3 (<0.1)	1 (<0.1)
Musculoskeletal disorder	3 (<0.1)	4 (<0.1)
Muscle hemorrhage	1 (<0.1)	0
Myosclerosis	1 (<0.1)	1 (<0.1)
Rhabdomyolysis	1 (<0.1)	0
Myopathy	0	1 (<0.1)
Injury, poisoning, and procedural complications	**112 (1.3)**	**154 (1.7)**
Muscle strain	99 (1.1)	133 (1.5)
Muscle injury	14 (0.2)	20 (0.2)
Muscle rupture	2 (<0.1)	2 (<0.1)

[a] AE number in this table are all AEs occurring during the randomized treatment period and not just treatment-emergent AEs
Source: Applicant's Table 38, Pg 93, CSR JUPITER

Skeletal muscle biochemistry

Myopathy was defined as muscle aches or weakness in conjunction with an increase in CK >10x ULN and was recorded as an adverse event. If markedly elevated CK levels (>10x ULN) were accompanied by unexplained muscle pain, tenderness, or weakness, trial therapy was to have been discontinued.

During the randomized-treatment phase of JUPITER, there were 2 rosuvastatin-treated subjects and 1 placebo-treated subject with CK elevations >10x ULN which was predefined as a clinically significant laboratory event. Of the subjects with a CK >10x ULN, there were no concomitant increases in creatinine levels to suggest kidney injury.

Table 46: Subjects with CK >10x ULN (1200 U/L) in randomized treatment phase of JUPITER (ITT population)

Subject	Treatment	Age/ Race/Sex	Visit	Days from randomization	CK (U/L)	Creatinine (mg/dL)	Comments
1241-0002	Rosuva 20 mg	60 W/M	Week-4	-28	63	1.0	1 month before CK levels drawn, had muscle spasm (back) AE for 4 days
			Final visit	1638	2874	0.9	
7651-0133	Rosuva 20 mg	M	Week-4	-25	46		Two hours a day of vigorous exercise previous 3 weeks. No symptoms
			Final visit	597	11404	1.0	
6042-0013	Placebo	63 B/M	Week-4	-27	152	1.1	AE of paresthesia started Day
			Final	687	1588	1.3	

Subject	Treatment	Age/ Race/Sex	Visit	Days from randomization	CK (U/L)	Creatinine (mg/dL)	Comments
			visit				71 and was ongoing throughout study

Source: Applicant's Table 11.3.7.2.21, Pg 77939, Table 11.36.3 Pg 34941, CSR JUPITER

At the final visit, the CK values for the rosuvastatin-treated group had increased by a mean of 11.1 U/L and in the placebo-treated group by a mean of 2.3 U/L. The difference in mean CK values between the two groups at the final visit was approximately 8.0 U/L.

Renal adverse events

In JUPITER there were a greater number of renal-related AEs in the rosuvastatin group (535/8901, 6.0%) as compared to the placebo group (480/8901, 5.4%). Of the renal AEs, hematuria and proteinuria were the most commonly occurring AEs with a higher incidence in the rosuvastatin treatment group. Acute, chronic, and unspecified renal failure occurred with similar frequency in the 2 treatment groups.

Table 47: Number and percentage of subjects with renal-related adverse events reported during the randomized treatment phase, by SOC and preferred term (ITT population)

System Organ Class Preferred Term	Rosuvastatin N=8901 n (%)	Placebo N=8901 n (%)
Any renal-related AE	**535 (6.0)**	**480 (5.4)**
Investigations	110 (1.2)	93 (1.0)
Urine analysis abnormal	40 (0.4)	43 (0.5)
Blood creatinine increased	39 (0.4)	30 (0.3)
Red blood cells urine	18 (0.2)	12 (0.1)
Blood urea increased	5 (0.1)	1 (<0.1)
Protein urine present	5 (0.1)	8 (0.1)
Glomerular filtration rate decreased	3 (<0.1)	1 (<0.1)
Urine output decreased	3 (<0.1)	0
Blood urine present	2 (<0.1)	1 (<0.1)
Protein urine	2 (<0.1)	0
Red blood cells urine positive	2 (<0.1)	0
Urine color abnormal	1 (<0.1)	0
Renal and urinary disorders	452 (5.1)	406 (4.6)
Hematuria	241 (2.7)	203 (2.3)
Proteinuria	149 (1.7)	127 (1.4)
Renal failure	25 (0.3)	23 (0.3)
Renal failure chronic	23 (0.3)	28 (0.3)
Renal failure acute	19 (0.2)	16 (0.2)
Renal impairment	11 (0.1)	8 (0.1)
Urine flow decreased	8 (0.1)	15 (0.2)
Renal disorder	5 (0.1)	4 (<0.1)
Microalbuminuria	4 (<0.1)	3 (<0.1)

System Organ Class Preferred Term	Rosuvastatin N=8901 n (%)	Placebo N=8901 n (%)
Azotemia	3 (<0.1)	2 (<0.1)
Anuria	2 (<0.1)	1 (<0.1)
Oliguria	2 (<0.1)	1 (<0.1)
Urine odor abnormal	2 (<0.1)	1 (<0.1)
Glomerulonephritis	1 (<0.1)	1 (<0.1)
Nephritis	1 (<0.1)	0
Nephrotic syndrome	1 (<0.1)	0
Hemoglobinuria	0	1 (<0.1)
Kidney fibrosis	0	1 (<0.1)
Renal atrophy	0	1 (<0.1)
Metabolism and nutrition disorders	3 (<0.1)	2 (<0.1)
Metabolic acidosis	2 (<0.1)	2 (<0.1)
Acidosis	1 (<0.1)	0
Source: Applicant's Table 39, Pg 95 CSR JUPITER		

Renal biochemistry

The number and percent of subjects with serum creatinine elevations increased >100% above baseline in the randomized treatment phase are listed in the following table.

Table 48: Serum creatinine elevations increased >100%

Serum creatinine (µmol/L)	Rosuvastatin 20 mg (N=7450) n (%)	Placebo (N=7410) n (%)
Creatinine >100% above baseline	10 (0.1)	6 (0.1)
Source: Applicant's Table 45, Pg 102 CSR JUPITER		

Urinalysis was performed at baseline and every 6 months during follow-up. The following table lists the urine dipstick protein and blood values at baseline and at the final visit in both treatment groups. Shifts in the amount of blood and protein in subject's urine were similar between the treatment groups.

Table 49: Urine dipstick protein and blood at Baseline and Final visit

	Rosuvastatin 20 mg (N=8901)		Placebo (N=8901)	
	Baseline n (%)	Final n (%)	Baseline n (%)	Final n (%)
Urine protein				
0	7223 (81.1)	5526 (62.1)	7256 (81.5)	5585 (62.7)
Trace	1063 (11.9)	970 (10.9)	1052 (11.8)	941 (10.6)
+	432 (4.9)	507 (5.7)	447 (5.0)	420 (4.7)
++	123 (1.4)	135 (1.5)	99 (1.1)	105 (1.2)
+++	16 (0.2)	22 (0.2)	11 (0.1)	20 (0.2)
++++	1 (<0.1)	2 (<0.1)	3 (<0.1)	2 (<0.1)
NR	40 (0.4)	8 (0.1)	30 (0.3)	3 (<0.1)
Urine blood				
0	7924 (89.0)	6244 (70.1)	7909 (88.9)	6280 (70.6)
Trace	487 (5.5)	465 (5.2)	489 (5.5)	406 (4.6)
+	268 (3.0)	244 (2.7)	273 (3.1)	223 (2.5)

	Rosuvastatin 20 mg (N=8901)		Placebo (N=8901)	
	Baseline n (%)	Final n (%)	Baseline n (%)	Final n (%)
++	118 (1.3)	145 (1.6)	137 (1.5)	111 (1.2)
+++	62 (0.7)	65 (0.7)	60 (0.7)	55 (0.6)
NR	39 (0.4)	7 (0.1)	30 (0.3)	1 (<0.1)

a +30; ++ 100; +++300; ++++ ≥2000 mg/dL; NR Not recorded
b + small; ++ moderate; +++large; NR Not recorded
Source: Applicant's Table 46, Pg 103 CSR JUPITER

Renal function

Estimated GFR

The mean estimated GFR (eGFR) was similar in the treatment groups at baseline. Both groups experienced a decrease in eGFR during follow-up. Mean eGFR fell less in the rosuvastatin group. The eGFR fell from baseline -7.23 ml/min/1.73 m^2 in the rosuvastatin group versus -7.72 ml/min/1.73 m^2 in the placebo group.

In both groups the majority of subjects (64.3% rosuvastatin, 63.7% placebo) at baseline had an eGFR that fell within the definition of mild impairment (60 to <90 ml/min/1.73 m^2). An estimated GFR was considered normal at ≥ 90 ml/min/1.73 m^2. Both treatment groups experienced a similar frequency of shifts in eGFR. No subject treated with rosuvastatin with a normal eGFR at baseline had a clinically significant reduction in eGFR (<30 ml/min/1.73 m^2).

Creatinine clearance

The majority of subjects in both treatment groups had a creatinine clearance in the normal (>80 ml/min) to mildly impaired range (50 to ≤ 80 ml/min). There were no significant differences between treatment groups at baseline or final visit. Shifts in mean creatinine clearance were similar among the rosuvastatin and placebo treatment groups.

Neuropsychiatric adverse events

Due to the concern over statin use and neurocognitive adverse effects, including memory impairment, memory loss, and confusion, as well as depression and anxiety, selected nervous system and psychiatric disorder adverse events were examined. Please note Table 50 does not include all nervous system and psychiatric disorder AEs experienced in the JUPITER trial.

Table 50: JUPITER Number and percentage of subjects with selected nervous system and psychiatric disorders adverse events reported during the randomized treatment phase, by SOC and preferred term (ITT population)

SOC Preferred Term	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Any adverse event	**568 (6.4)**	**586 (6.6)**
Nervous system disorders	**69 (0.8)**	**76 (0.9)**

Amnesia	30 (0.3)	33 (0.4)
Memory impairment	18 (0.2)	16 (0.2)
Dementia	12 (0.1)	9 (0.1)
Dementia Alzheimer's type	7 (0.1)	7 (0.1)
Disturbance in attention	3 (<0.1)	1 (<0.1)
Amnestic disorder	2 (<0.1)	1 (<0.1)
Global amnesia	2 (<0.1)	1 (<0.1)
Senile dementia	1 (<0.1)	2 (<0.1)
Cognitive disorder	0	6 (0.1)
Vascular dementia	0	1 (<0.1)
Psychiatric disorders	**515 (5.8)**	**533 (6.0)**
Insomnia	226 (2.5)	208 (2.3)
Depression	184 (2.1)	214 (2.4)
Anxiety	128 (1.4)	157 (1.8)
Confusional state	18 (0.2)	4 (<0.1)
Depressed mood	12 (0.1)	12 (0.1)
Nervousness	8 (0.1)	7 (0.1)
Generalized anxiety disorder	2 (<0.1)	1 (<0.1)
Major depression	2 (<0.1)	0
Suicidal ideation	2 (<0.1)	0
Completed suicide	1 (<0.1)	1 (<0.1)
Suicide attempt	1 (<0.1)	0
Depression suicidal	0	1 (<0.1)
Depressive symptom	0	1 (<0.1)
Initial insomnia	0	1 (<0.1)
Personality change	0	1 (<0.1)
Source: IR response Applicant Table 11.36.1.1.7B		

The Applicant reported that 18 rosuvastatin-treated subjects versus 4 placebo-treated subjects experienced the AE of "confusional state". Six of the 18 confusional states in rosuvastatin-treated subjects were considered as a SAE. Two subjects were not on study medication at the time and others had concurrent medical conditions and/or medications ongoing at the time of the event. The following table provides further details of the rosuvastatin-treated subjects experiencing the confusional adverse events.

Table 51: Description of rosuvastatin-treated subjects experiencing AE of confusional state

Center	Subject ID	Age	Sex	Verbatim term as reported	Day of study event occurred	Overall duration of treatment with study medication (days)	Medications listed at time of event	Comments
1031	0031	76	F	Confusion	670	1247	Prevacid, Donnatal, Morphine, Zofran, Maalox, Tylenol, Dilaudid	Concurrent with AE of confusional state had abdominal pain, N/V, fever diagnosed with infective cholecystitis requiring hospitalization and surgery
1244	0018	55	M	Intermittent confusion	Not on rosuva at time of event	722	Digoxin, amiodarone, ASA	Current medical history of atrial fibrillation and PMH of depression. Discontinued study medication on Day 722 due to elevated CK and myalgia. One year later experienced concurrent with intermittent confusion, intermittent chest spasms, headache, dyspnea, constipation, and depression
1282	0013	74	M	Confusion	1190	1269	ASA, Penicillin, Coumadin, Lanoxin, Warfarin, Lisinopril, Accupril, Zyrtec, Diovan	Prior AEs experienced within 6 months of event: Day 1069: Fall with scalp laceration, Day 1101 Anxiety, Day 1136 UTI with kidney stone
1668	0124	82	F	Confusion	250	607	Aleve, HCTZ, KCL	Day 196 AE of frontal meningioma. Eight days prior to event experienced the AE of Fall and Left shoulder strain with nerve impingement.
1802	0113	87	M	Confusion (SAE)	79	373	PPI, Atenolol/HCTZ, Ramipril, Lorazepam, benadryl, ibuprofen, clopidogrel sulfate, KCL	Hx of BPH, GI bleed, peptic ulcer, renal insufficiency, rhinitis. Admitted to hospital after daughter found at home disoriented and confused. On admission, neuro exam was benign, and he was alert and oriented. Head CT neg, EKG sinus rhythm, multiple premature atrial complexes, left anterior fascicular block, probable old anteroseptal infarct, CXR lungs clear. Discharged two days later to subacute rehab facility
2067	0021	84	F	Confusion	Not on rosuvastatin at time of event	186	ASA, Calcium	Experienced concurrent AE of depression. Later started on Remeron for depression and Geodon

Center	Subject ID	Age	Sex	Verbatim term as reported	Day of study event occurred	Overall duration of treatment with study medication (days)	Medications listed at time of event	Comments
2249	0001	69	F	Confusion	12	1167	Glucosamine, Actonel	Had AE of light-headedness and muscular weakness prior to randomization. Experienced concurrent AEs of urinary hesitation, bronchitis, and blurred vision (levaquin)
2324	0019			Confusion (SAE)	327	327	Levothyroid, Prozac, HCTZ, Losartan, Oxybutynin	Hospitalized due to joint pain exacerbation and confusion, and leukocytosis for 5 days. The subject showed signs of confusion when trying to explain to hospital staff about her study therapy. Study therapy was discontinued and the subject was started on lovastatin. Events noted in discharge summary included acute renal failure, bilateral Babinski signs, and possible small right posterior communicating aneurysm
4010	0060	72	M	Confusion	250	246	Flovent, Ventolin, Metoprolol, Gravol (for N/V)	Brought to ER with back pain, tachycardia, and hypotension. Diagnosed with contained abdominal aneurysm rupture. Repair on Day 247, Concurrent AE of pneumonia on Day 250
4048	0074	77	M	Confusion	377	725	Rivasa, Viagra, Prevacid, Prinivil, Efudex, Warfarin, Lanoxin, Diltiazem, Tapazole,	Hospitalized for the concurrent AE of pericarditis and pericardial effusion. Morphine listed as concurrent medication on same day as confusional state. Experienced a second AE of confusional state on Day 387 with concurrent AE of pericardial effusion which required hospitalization
4099	0006	70	M	Confusion	454	1616	Dyazide, Ativan, Clonazepam	Concurrent AEs of depression, insomnia, anxiety, Parkinson's disease
4141	0044	74	M	Confusion	Not on rosuva at time of event	302	Indocid, Norvasc, Meloxicam, Percocet, Tylenol #3	Off rosuvastatin at time of event. Experienced concurrent AE of muscle weakness, Percocet and Tylenol #3 for bilateral hip pain listed as concurrent medication on day of confusional state. AE reported 15 days later of diffuse large B-cell lymphoma
5001	1388	62	M	Confusion is due to opioid use (SAE)	591	819	Morphine	Admitted to hospital due to pain at sternotomy wound and confusion secondary to increase opioid use. Condition improved after morphine stopped.

Center	Subject ID	Age	Sex	Verbatim term as reported	Day of study event occurred	Overall duration of treatment with study medication (days)	Medications listed at time of event	Comments
5007	0782	74	F	Confusion (SAE)	655	726	Nifedipine, ASA, Indapamide, erythromycin, amoxicillin	Patient admitted to hospital with mild confusion. Diagnosed with hyponatremia, hypokalemia secondary to thiazide diuretic and mild normocytic anemia, Investigations showed signs of UTI and weight loss
5037	0069	76	M	Intermittent confusion	Not on treatment at time of event	79	Diclofenac, tramadol, paracetamol	Off treatment at time of event. Experienced TIA within 2 months of event
6410	0023	81	M	Acute confusional state (SAE)	461	952	ASA	Hospitalized for acute confusional state, recovered. No neurological deficit or lab findings. Head CT normal. Study drug was continued. No concurrent AEs noted. Current illness of BPH, varicose veins, past med hx of osteoarthritis
7154	0002	77	M	Acute syndrome confusional	170	176	Amantadine, enalapril, ASA, Cardura, levothyroxine, ASA	Recently diagnosed with Parkinson's disease and had started amantadine. Hospitalized for acute confusional syndrome, presenting with visual hallucinations. Consulting neurologist felt the events were related to an increased dose of amantadine, while hospitalized diagnosed with nosocomial pneumonia and infective endocarditis prolonging hospitalization. Subject withdrew from study due to these events
8487	0008	82	F	Confused (SAE)	396	396	Sertraline, paracetamol, thiamine, omeprazole, brotizolam	Hospitalized with fever, confusional state, died of multi-organ failure/septic shock
Source: Applicant's Table 1 IR response 09 November 2009								

Neoplastic adverse events

Fatal events due to cancer

In JUPITER, there were a smaller number of Neoplasm SOC treatment-emergent adverse events leading to death in the rosuvastatin group (40/8901, 0.4%) versus the placebo group (65/8901, 0.7%). Overall, however, neoplastic adverse events were the leading cause of TEAE leading to death in both treatment groups. A similar pattern was also seen with Neoplasm SAEs. The following two tables list the number and frequency of treatment-emergent adverse events leading to death and non-fatal serious adverse events in the Neoplasm SOC.

Table 52 JUPITER: Number and percentage of subjects with TEAE leading to death in the Neoplasm SOC (ITT population)

System organ class Preferred Term	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Neoplasms benign, malignant, and unspecified (includes cysts and polyps)	**40 (0.4)**	**65 (0.7)**
Respiratory		
Bronchial carcinoma	3 (<0.1)	0
Lung neoplasm malignant	3 (<0.1)	8 (0.1)
Lung cancer metastatic	2 (<0.1)	2 (<0.1)
Non-small cell lung cancer	1 (<0.1)	1 (<0.1)
Small cell lung cancer stage unspecified	1 (<0.1)	3 (<0.1)
Mesothelioma	1 (<0.1)	0
Lung adenocarcinoma	0	1 (<0.1)
Lung adenocarcinoma metastatic	0	2 (<0.1)
Lung neoplasm	0	2 (<0.1)
Lung squamous cell carcinoma stage unspecified	0	1 (<0.1)
Small cell lung cancer metastatic	0	1 (<0.1)
Gastrointestinal/Hepatic		
Gastrointestinal carcinoma	2 (<0.1)	2 (<0.1)
Esophageal carcinoma	2 (<0.1)	1 (<0.1)
Pancreatic carcinoma	2 (<0.1)	2 (<0.1)
Colon cancer	1 (<0.1)	3 (<0.1)
Colon cancer metastatic	1 (<0.1)	3 (<0.1)
Esophageal adenocarcinoma	1 (<0.1)	1 (<0.1)
Oropharyngeal cancer stage unspecified	1 (<0.1)	0
Bile duct cancer recurrent	0	1 (<0.1)
Colon neoplasm	0	1 (<0.1)
Gastric cancer	0	1 (<0.1)
Gastrointestinal cancer metastatic	0	1 (<0.1)
Gastro-esophageal cancer	0	1 (<0.1)
Hepatic cancer metastatic	0	1 (<0.1)
Hepatic neoplasm malignant	0	1 (<0.1)
Metastases to liver	0	1 (<0.1)
Metastatic gastric cancer	0	1 (<0.1)
Esophageal cancer metastatic	0	2 (<0.1)
Pancreatic carcinoma metastatic	0	3 (<0.1)
Pancreatic neoplasm	0	1 (<0.1)
Pharyngeal cancer stage unspecified	0	1 (<0.1
Tongue neoplasm malignant stage unspecified	0	1 (<0.1)
Brain		

System organ class Preferred Term	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Brain neoplasm	2 (<0.1)	0
Astrocytoma	0	1 (<0.1)
Astrocytoma malignant	0	1 (<0.1)
Glioma	0	1 (<0.1)
Hematologic		
Acute leukemia	2 (<0.1)	0
Multiple myeloma	2 (<0.1)	2 (<0.1)
Acute myeloid leukemia	1(<0.1)	0
Myeloid leukemia	1 (<0.1)	0
Non-Hodgkin's lymphoma	1 (<0.1)	0
Skin		
Metastatic malignant melanoma	2 (<0.1)	0
Metastatic squamous cell carcinoma	0	1 (<0.1)
Renal		
Renal cancer metastatic	1 (<0.1)	0
Renal cell carcinoma	1 (<0.1)	1 (<0.1)
Metastatic renal cell carcinoma	0	2 (<0.1)
Renal neoplasm	0	1 (<0.1)
Reproductive/GU/Breast		
Uterine cancer	1 (<0.1)	0
Breast cancer metastatic	0	1 (<0.1)
Ovarian cancer	0	1 (<0.1)
Prostate cancer metastatic	0	1 (<0.1)
Endocrine		
Adenocarcinoma	1 (<0.1)	0
Neuroendocrine carcinoma	0	1 (<0.1)
Soft tissue/smooth muscle		
Leiomyosarcoma metastatic	1 (<0.1)	0
Sarcoma	0	1 (<0.1)
General		
Metastatic neoplasm	2 (<0.1)	0
Neoplasm malignant	1 (<0.1)	2 (<0.1)
Source: Applicant's Table 11.3.3.1.2.3, Pg 5604, CSR JUPITER		

Table 53: Number and percentage of subjects with treatment-emergent non-fatal SAE in the Neoplasm SOC (ITT population)[a]

System organ class	Events	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Neoplasms benign, malignant, and unspecified (includes cysts and polyps)		**258 (2.9)**	**261 (2.9)**
	Prostate cancer	37 (0.4)	41 (0.5)
	Breast cancer	21 (0.2)	24 (0.3)
	Colon cancer	20 (0.2)	22 (0.3)
	Basal cell carcinoma	12 (0.1)	6 (0.1)
	Lung neoplasm malignant	10 (0.1)	13 (0.1)
	Non-Hodgkin's lymphoma	9 (0.1)	3 (<0.1)
	Bladder cancer	6 (0.1)	9 (0.1)
	Endometrial cancer	6 (0.1)	1 (<0.1)
	Lung adenocarcinoma	5 (0.1)	2 (<0.1)
	Non-small cell lung cancer	5 (0.1)	1 (<0.1)
	Squamous cell carcinoma of skin	5 (0.1)	0
	Gastric cancer	4 (<0.1)	3 (<0.1)
	Lymphoma	4 (<0.1)	3 (<0.1)
	Malignant melanoma	4 (<0.1)	4 (<0.1)
	Renal cell carcinoma	4 (<0.1)	6 (0.1)
	Transitional cell carcinoma	4 (<0.1)	1 (<0.1)
	Breast cancer in situ	3 (<0.1)	1 (<0.1)
	Colon neoplasm	3 (<0.1)	0
	Gastrointestinal carcinoma	3 (<0.1)	4 (<0.1)
	Lung squamous cell carcinoma stage unspecified	3 (<0.1)	1 (<0.1)
	Pancreatic carcinoma	3 (<0.1)	4 (<0.1)
	Uterine cancer	3 (<0.1)	0
	Bladder neoplasm	2 (<0.1)	7 (0.1)
	Bronchial carcinoma	2 (<0.1)	0
	Chronic lymphocytic leukemia	2 (<0.1)	2 (<0.1)
	Colon adenoma	2 (<0.1)	2 (<0.1)
	Hepatic cancer metastatic	2 (<0.1)	0
	Hepatic neoplasm malignant	2 (<0.1)	1 (<0.1)
	Lung cancer metastatic	2 (<0.1)	1 (<0.1)
	Lung neoplasm	2 (<0.1)	6 (0.1)
	Meningioma	2 (<0.1)	1 (<0.1)
	Metastases to bone	2 (<0.1)	2 (<0.1)
	Metastases to liver	2 (<0.1)	0
	Myelodysplastic syndrome	2 (<0.1)	0
	Esophageal carcinoma	2 (<0.1)	8 (0.1)
	Ovarian cancer	2 (<0.1)	4 (<0.1)
	Pituitary tumor benign	2 (<0.1)	0
	Renal cancer	2 (<0.1)	1 (<0.1)
	Squamous cell carcinoma	2 (<0.1)	1 (<0.1)
	Thyroid neoplasm	2 (<0.1)	1 (<0.1)
	Ureteric cancer	2 (<0.1)	1 (<0.1)
	Acute myeloid leukemia recurrent	1 (<0.1)	0

System organ class	Events	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
	Acute myelomonocytic leukemia	1 (<0.1)	0
	Adrenal neoplasm	1 (<0.1)	0
	B-cell small lymphocytic lymphoma	1 (<0.1)	0
	Benign breast neoplasm	1 (<0.1)	0
	Benign colonic neoplasm	1 (<0.1)	0
	Benign salivary gland neoplasm	1 (<0.1)	0
	Bladder cancer recurrent	1 (<0.1)	0
	Bladder papilloma	1 (<0.1)	1 (<0.1)
	Bowen's disease	1 (<0.1)	1 (<0.1)
	Breast cancer metastatic	1 (<0.1)	0
	Carcinoid tumor of the small bowel	1 (<0.1)	0
	Cardiac myxoma	1 (<0.1)	0
	Cervix carcinoma stage III	1 (<0.1)	0
	Cholesteatoma	1 (<0.1)	0
	Colon cancer stage I	1 (<0.1)	0
	Diffuse large B-cell lymphoma	1 (<0.1)	0
	Ganglioneuroma	1 (<0.1)	0
	Gastrointestinal cancer metastatic	1 (<0.1)	0
	Gastrointestinal stromal tumor	1 (<0.1)	0
	Gastroesophageal cancer	1 (<0.1)	0
	Head and neck cancer	1 (<0.1)	0
	Hodgkin's disease	1 (<0.1)	1 (<0.1)
	Large cell carcinoma of the respiratory tract stage unspecified	1 (<0.1)	0
	Laryngeal cancer	1 (<0.1)	1 (<0.1)
	Leiomyosarcoma metastatic	1 (<0.1)	0
	Leukemia	1 (<0.1)	2 (<0.1)
	Lip and/or oral cavity cancer	1 (<0.1)	0
	Lipoma	1 (<0.1)	2 (<0.1)
	Lung carcinoma cell type unspecified stage III	1 (<0.1)	0
	Metastatic malignant melanoma	1 (<0.1)	0
	Metastatic neoplasm	1 (<0.1)	0
	Metastatic renal cell carcinoma	1 (<0.1)	1 (<0.1)
	Multiple myeloma	1 (<0.1)	2 (<0.1)
	Myeloid leukemia	1 (<0.1)	0
	Nasopharyngeal cancer	1 (<0.1)	0
	Neurilemmoma	1 (<0.1)	0
	Neuroendocrine carcinoma of the skin	1 (<0.1)	0
	Neurofibroma	1 (<0.1)	0
	Non-Hodgkin's lymphoma recurrent	1 (<0.1)	0
	Ocular neoplasm	1 (<0.1)	0
	Esophageal adenocarcinoma	1 (<0.1)	1 (<0.1)

System organ class	Events	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
	Esophageal squamous cell carcinoma	1 (<0.1)	0
	Oropharyngeal cancer stage unspecified	1 (<0.1)	0
	Ovarian adenoma	1 (<0.1)	0
	Ovarian neoplasm	1 (<0.1)	2 (<0.1)
	Pelvic neoplasm	1 (<0.1)	0
	Penis carcinoma	1 (<0.1)	0
	Polycythemia vera	1 (<0.1)	0
	Prostate cancer recurrent	1 (<0.1)	1 (<0.1)
	Prostatic adenoma	1 (<0.1)	0
	Pseudomyxoma peritonei	1 (<0.1)	0
	Rectal cancer	1 (<0.1)	8 (0.1)
	Rectosigmoid cancer	1 (<0.1)	0
	Renal cancer metastatic	1 (<0.1)	0
	Renal neoplasm	1 (<0.1)	0
	Rhabdomyosarcoma	1 (<0.1)	0
	Signet-ring cell carcinoma	1 (<0.1)	0
	Skin cancer	1 (<0.1)	0
	T-cell lymphoma	1 (<0.1)	0
	Testis cancer	1 (<0.1)	0
	Throat cancer	1 (<0.1)	0
	Thyroid cancer	1 (<0.1)	2 (<0.1)
	Tongue neoplasm malignant stage unspecified	1 (<0.1)	0
	Ureteric cancer metastatic	1 (<0.1)	0
	Waldenstrom's macroglobulinemia	1 (<0.1)	3 (<0.1)

[a] This table only includes preferred terms that occurred in the rosuvastatin-treated group
Source: Applicant's Table 11.3.4.1.2.2, Pg 8356 CSR JUPITER

In JUPITER, the overall incidence of Neoplasm SOC treatment-emergent adverse events was 6.8% in the rosuvastatin-treated group and 7.6% in the placebo-treated group. Of these AEs, only basal cell carcinoma reached a frequency of 1% in the rosuvastatin group compared with 0.9% in the placebo group. There was a similar frequency of Neoplasm TEAE in both treatment groups.

To address the concern regarding low LDL-C levels and cancer, of subjects with a LDL-C less than 50 mg/dL 2.5% (104/4154) in the rosuvastatin group and 3.9% (9/232) in the placebo group experienced a treatment-emergent SAE in the Neoplasm SOC group.

JUPITER Safety conclusions

- There were a total of 320 treatment-emergent AEs leading to death in the JUPITER trial (1.6% in rosuvastatin group versus 2.0% in the placebo group).
- An imbalance was noted in the number of deaths in the Gastrointestinal SOC with 13 TEAE deaths in the rosuvastatin group compared to 1 TEAE death in the placebo group. Based on FDA review of the information supplied by the Applicant, this imbalance is considered a chance finding.
- Discontinuations of study medication due to an AE were similar between treatment groups. Three times as many subjects in the placebo group compared with the rosuvastatin group discontinued study treatment to initiate open-label statin treatment.
- Withdrawal from study participation in JUPITER was also similar between treatment groups. Musculoskeletal disorders were the most common reason for study withdrawal in both treatment groups.
- There was a 27% increase in investigator-reported diabetes in the rosuvastatin-treatment group compared to the placebo-treatment group.
- A post-hoc analysis of development of diabetes defined by either a HbA1c >6.5%, a fasting glucose value of ≥ 126 mg/dL, or both demonstrated a greater incidence of diabetes in the rosuvastatin-treatment group (15.3%) than in the placebo-treatment group (12.0%).
- Overall hepatic, skeletal, and renal-related AEs occurred with similar frequencies between treatment groups.
- A higher percentage of rosuvastatin-treated subjects experienced an ALT >3x ULN and a small percentage experienced an ALT >3x ULN on 2 consecutive occasions. No Hy's law cases were observed in a rosuvastatin-treated subject.
- Muscle-related AEs occurred at a higher incidence in the rosuvastatin treatment group compared to the placebo group. Myalgia was the most commonly reported preferred term in the rosuvastatin (8.0%) and placebo groups (7.2%). There was one case of rhabdomyolysis in JUPITER in a rosuvastatin-treated subject, a 90 year-old man with influenza and inability to arise from the floor for ~24 hours, secondary to weakness.
- CK >10x ULN occurred in 2 rosuvastatin-treated subjects and 1 placebo-treated subject.
- Hematuria and proteinuria were the most commonly-occurring Renal and Urinary Disorder SOC AEs with a higher incidence in the rosuvastatin treatment group (4.4%) than in the placebo treatment group (3.7%). Acute, chronic, and unspecified renal failure occurred with similar frequency in the 2 treatment groups.
- Of the selected neuropsychiatric-related AEs, an imbalance in confusional state was observed, with 18 cases reported in the rosuvastatin group and 4 cases in the placebo group.
- The overall incidence of Neoplasm SOC treatment-emergent AEs was 6.8% in the rosuvastatin-treated group and 7.6% in the placebo-treated group. Of these AEs, only basal cell carcinoma reached a frequency of 1% of the population in the rosuvastatin group compared with 0.9% in the placebo group.
- In subjects with an on-study LDL-C less than 50 mg/dL, 2.5% (104/4154) in the rosuvastatin group and 3.9% (9/232) in the placebo group experienced a treatment-emergent SAE in the Neoplasm SOC.

Appendices

Appendix A: NCEP ATPIII At a Glance Guidelines

National Cholesterol Education Program

ATP III Guidelines At-A-Glance Quick Desk Reference

Step 1

Determine lipoprotein levels–obtain complete lipoprotein profile after 9- to 12-hour fast.

ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

LDL Cholesterol – Primary Target of Therapy	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high
Total Cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High

Step 2

Identify presence of clinical atherosclerotic disease that confers high risk for coronary heart disease (CHD) events (CHD risk equivalent):

- Clinical CHD
- Symptomatic carotid artery disease
- Peripheral arterial disease
- Abdominal aortic aneurysm.

Step 3

Determine presence of major risk factors (other than LDL):

Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals

Cigarette smoking
Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
Low HDL cholesterol (<40 mg/dL)*
Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
Age (men ≥45 years; women ≥55 years)

** HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.*

- Note: in ATP III, diabetes is regarded as a CHD risk equivalent.

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Step 4

If 2+ risk factors (other than LDL) are present without CHD or CHD risk equivalent, assess 10-year (short-term) CHD risk (see Framingham tables).
Three levels of 10-year risk:

- >20% — CHD risk equivalent
- 10-20%
- <10%

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Step 5

Determine risk category:

- Establish LDL goal of therapy
- Determine need for therapeutic lifestyle changes (TLC)
- Determine level for drug consideration

LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

* *Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.*
† *Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.*

Appendix B: Framingham Tables used with NCEP ATPIII guidelines

Men

Estimate of 10-Year Risk for Men

(Framingham Point Scores)

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Point Total	10-Year Risk %
<0	< 1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥ 30

10-Year risk _____%

Women

Estimate of 10-Year Risk for Women

(Framingham Point Scores)

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Point Total	10-Year Risk %
< 9	< 1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥ 30

10-Year risk _____%

Appendix C: NCEP ATP III 2004 Update

TABLE 2. ATP III LDL-C Goals and Cutpoints for TLC and Drug Therapy in Different Risk Categories and Proposed Modifications Based on Recent Clinical Trial Evidence

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy**
High risk: CHD* or CHD risk equivalents† (10-year risk >20%)	<100 mg/dL (optional goal: <70 mg/dL)‖	≥100 mg/dL#	≥100 mg/dL†† (<100 mg/dL: consider drug options)**
Moderately high risk: 2+ risk factors‡ (10-year risk 10% to 20%)§§	<130 mg/dL¶	≥130 mg/dL#	≥130 mg/dL (100–129 mg/dL; consider drug options)‡‡
Moderate risk: 2+ risk factors‡ (10-year risk <10%)§§	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk: 0–1 risk factor§	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)

*CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.

†CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with 10-year risk for hard CHD >20%.

‡Risk factors include cigarette smoking, hypertension (BP ≥140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men ≥45 years; women ≥55 years).

§§Electronic 10-year risk calculators are available at www.nhlbi.nih.gov/guidelines/cholesterol.

§Almost all people with zero or 1 risk factor have a 10-year risk <10%, and 10-year risk assessment in people with zero or 1 risk factor is thus not necessary.

‖Very high risk favors the optional LDL-C goal of <70 mg/dL, and in patients with high triglycerides, non-HDL-C <100 mg/dL.

¶Optional LDL-C goal <100 mg/dL.

#Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL-C level.

**When LDL-lowering drug therapy is employed, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

††If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglycerides or low HDL-C, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

‡‡For moderately high-risk persons, when LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial results.

TABLE 3. Recommendations for Modifications to Footnote the ATP III Treatment Algorithm for LDL-C

- Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. TLC has the potential to reduce cardiovascular risk through several mechanisms beyond LDL lowering.
- In high-risk persons, the recommended LDL-C goal is <100 mg/dL.
  - An LDL-C goal of <70 mg/dL is a therapeutic option on the basis of available clinical trial evidence, especially for patients at very high risk.
  - If LDL-C is ≥100 mg/dL, an LDL-lowering drug is indicated simultaneously with lifestyle changes.
  - If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug to achieve an LDL-C level <70 mg/dL is a therapeutic option on the basis of available clinical trial evidence.
  - If a high-risk person has high triglycerides or low HDL-C, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. When triglycerides are ≥200 mg/dL, non-HDL-C is a secondary target of therapy, with a goal 30 mg/dL higher than the identified LDL-C goal.
- For moderately high-risk persons (2+ risk factors and 10-year risk 10% to 20%), the recommended LDL-C goal is <130 mg/dL; an LDL-C goal <100 mg/dL is a therapeutic option on the basis of available clinical trial evidence. When LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial evidence.
- Any person at high risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglyceride, low HDL-C, or metabolic syndrome) is a candidate for TLC to modify these risk factors regardless of LDL-C level.
- When LDL-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.
- For people in lower-risk categories, recent clinical trials do not modify the goals and cutpoints of therapy.

Appendix D: Definition of clinical endpoints

Cardiovascular causes of death

- Myocardial infarction: Fatal event fulfilling prespecified diagnostic criteria of nonfatal MI, diagnosis of MI stated in hospital discharge records, death certificate, or from autopsy evidence.
- Heart failure: cannot be classified as due to MI and no other obvious cause
- Stroke: Fatal event fulfilling prespecified diagnostic criteria of nonfatal stroke, diagnosis of stroke stated in hospital discharge records, death certificate, or from autopsy evidence.
- Sudden death: Cannot be classified as being due to MI or stroke and the event is instantaneous or occurs within 12 hours of onset of acute chest pain, syncope, pulmonary edema, cardiogenic shock, or other cardiovascular or cerebrovascular symptoms.

Nonfatal Stroke

- Unequivocal signs of a focal or global neurologic deficit with sudden onset and of duration >24 hours. Computed tomography (CT) and/or magnetic resonance imaging (MRI) scans and clinical reports will classify stroke as hemorrhagic, thromboembolic, or other.

Nonfatal Myocardial Infarction

The diagnosis of nonfatal MI was made if at least two of the following criteria were met.

- Ischemic chest pain of more than 15 minutes duration with onset during the previous 48 hours, or pulmonary edema without previously known valvular disease, or shock without suspicion of acute hypovolemia
- A transient rise of serum CK, CK-MB, cardiac troponin, or any other clinically accepted marker of myocardial injury to values above the locally defined level for diagnosis of MI
- Development or disappearance of localized ST elevation ≥ 1 mm, combined with the development of persistent T-wave inversion in at least two anatomically contiguous standard ECG leads or development of new left bundle branch block

Unstable angina

Evidence of ischemic chest pain at rest or with minimal exertion, representing a change in subject's usual symptom pattern, which occurs within the preceding 48 hours, and requires hospitalization and presence of objective evidence of ischemia. Myocardial ischemia to be defined by at least one of the following criteria:

- New and/or dynamic ST depression (>0.5 mm), elevation (>1 mm) or T wave inversion (≥ 3 mm) on resting ECG
- A definite persistent or reversible wall motion abnormality or scintigraphic perfusion defect demonstrated either spontaneously or by stress testing
- Angiographic evidence of an epicardial coronary artery stenosis of ≥ 80% diameter reduction (or > 50% for the left main coronary artery) and/or evidence for intraluminal arterial thrombus

- A transient elevation of serum CK, CK-MB, troponin, or any other accepted marker of myocardial ischemia to a level greater than normal but less than the locally defined decision level for the diagnosis of MI.

Arterial Revascularization

Confirmed by hospital records demonstrating either of the following:

- Coronary artery bypass graft (CABG) surgery or bypass grafting of any peripheral artery or carotid
- At least one percutaneous transluminal intervention (PTI) including either angioplasty, stent placement, or other intravascular procedure involving coronary carotid or peripheral arteries.

Definition of Secondary Endpoint

Diabetes mellitus

The secondary endpoint definition of incident diabetes mellitus will be based upon physician diagnosis, new use of insulin or an oral hypoglycemic agent, evidence of a positive glucose tolerance test, or evidence of repeated fasting glucose greater than 126 mg/dL, or random glucose >200 mg/dL with symptoms of polyuria, polydipsia, and weight loss.

Venous thrombosis and/or pulmonary embolism

Diagnosis was confirmed based on venous ultrasonograms, angiograms, ventilation perfusion studies, computed tomography, and prescriptive evidence of new use of anticoagulation therapy.

Appendix E: MedDRA terms for diabetes

MedDRA SMQ Version 11.1 "narrow" hyperglycemia/new onset diabetes mellitus preferred terms used in analysis of METEOR, CORONA, and AURORA trials of diabetes-related AEs.

SMQ Name	Preferred Term	System Organ Class	High Level Group Term	High Level Term	PT Code
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood glucose increased	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10005557
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Diabetes complicating pregnancy	Pregnancy, puerperium and perinatal conditions	Maternal complications of pregnancy	Pregnancy complicated by maternal disorders	10012596
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Diabetes mellitus	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10012601
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Diabetes mellitus inadequate control	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10012607
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Diabetes with hyperosmolarity	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10012631
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Diabetic coma	Nervous system disorders	Neurological disorders NEC	Coma states	10012650
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Diabetic hyperglycaemic coma	Nervous system disorders	Neurological disorders NEC	Coma states	10012668
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Diabetic hyperosmolar coma	Nervous system disorders	Neurological disorders NEC	Coma states	10012669
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Diabetic ketoacidosis	Metabolism and nutrition disorders	Diabetic complications	Diabetic complications NEC	10012671
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Diabetic ketoacidotic hyperglycaemic coma	Nervous system disorders	Neurological disorders NEC	Coma states	10012672
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Fructosamine increased	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10017395
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Gestational diabetes	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10018209

Hyperglycaemia/new onset diabetes mellitus (SMQ)	Glucose tolerance impaired	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10018429
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Glucose tolerance impaired in pregnancy	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10018430
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Glycosuria	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalities	10018473
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Glycosuria during pregnancy	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalities	10018475
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Glucose urine present	Investigations	Renal and urinary tract investigations and urinalyses	Urinalysis NEC	10018478
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Glycosylated haemoglobin increased	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10018484
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hyperglycaemia	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10020635
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Insulin resistance	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10022489
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Insulin resistance syndrome	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10022490
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Insulin resistant diabetes	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10022491
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Ketoacidosis	Metabolism and nutrition disorders	Acid-base disorders	Metabolic acidoses (excl diabetic acidoses)	10023379
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Ketonuria	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalities	10023388
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Ketosis	Metabolism and nutrition disorders	Acid-base disorders	Metabolic acidoses (excl diabetic acidoses)	10023391

Hyperglycaemia/new onset diabetes mellitus (SMQ)	Neonatal diabetes mellitus	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10028933
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Pancreatogenous diabetes	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10033660
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Metabolic syndrome	Metabolism and nutrition disorders	Metabolism disorders NEC	Metabolic disorders NEC	10052066
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Insulin-requiring type 2 diabetes mellitus	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10053247
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Impaired fasting glucose	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10056997
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Urine ketone body present	Investigations	Metabolic, nutritional and blood gas investigations	Metabolism tests NEC	10057597
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hyperglycaemic hyperosmolar nonketotic syndrome	Metabolism and nutrition disorders	Diabetic complications	Diabetic complications neurological	10063554
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood 1,5-anhydroglucitol decreased	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10065367
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Latent autoimmune diabetes in adults	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10066389
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Type 1 diabetes mellitus	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10067584
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Type 2 diabetes mellitus	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10067585

MedDRA SMQ Version 11.1 "broad" hyperglycemia/new onset diabetes mellitus preferred terms (highlighted) used in analysis of METEOR, CORONA, and AURORA trials of diabetes-related AEs.

SMQ Name	Preferred Term	System Organ Class	High Level Group Term	High Level Term	PT Code
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Abnormal loss of weight	Metabolism and nutrition disorders	Appetite and general nutritional disorders	General nutritional disorders NEC	10000159
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Abnormal weight gain	Metabolism and nutrition disorders	Appetite and general nutritional disorders	General nutritional disorders NEC	10000188
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Acidosis	Metabolism and nutrition disorders	Acid-base disorders	Mixed acid-base disorders	10000486
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Altered state of consciousness	Nervous system disorders	Neurological disorders NEC	Disturbances in consciousness NEC	10001854
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood cholesterol increased	Investigations	Lipid analyses	Cholesterol analyses	10005425
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood glucose abnormal	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10005554
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood insulin abnormal	Investigations	Endocrine investigations (incl sex hormones)	Gastrointestinal, pancreatic and APUD hormone analyses	10005606
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood insulin decreased	Investigations	Endocrine investigations (incl sex hormones)	Gastrointestinal, pancreatic and APUD hormone analyses	10005613
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood lactic acid increased	Investigations	Metabolic, nutritional and blood gas investigations	Blood gas and acid base analyses	10005635
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood osmolarity increased	Investigations	Water, electrolyte and mineral investigations	Water and electrolyte analyses NEC	10005697
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood triglycerides increased	Investigations	Lipid analyses	Triglyceride analyses	10005839
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Body mass index decreased	Investigations	Physical examination topics	Physical examination procedures	10005895
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Body mass index increased	Investigations	Physical examination topics	Physical examination procedures	10005897

Hyperglycaemia/new onset diabetes mellitus (SMQ)	Coma	Nervous system disorders	Neurological disorders NEC	Coma states	10010071
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Dehydration	Metabolism and nutrition disorders	Electrolyte and fluid balance conditions	Total fluid volume decreased	10012174
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Depressed level of consciousness	Nervous system disorders	Neurological disorders NEC	Disturbances in consciousness NEC	10012373
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Glucose tolerance decreased	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10018428
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Glucose tolerance test abnormal	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10018433
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hunger	General disorders and administration site conditions	General system disorders NEC	Feelings and sensations NEC	10020466
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hypercholesterolaemia	Metabolism and nutrition disorders	Lipid metabolism disorders	Elevated cholesterol	10020603
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hyperlactacidaemia	Metabolism and nutrition disorders	Acid-base disorders	Metabolic acidoses (excl diabetic acidoses)	10020660
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hyperosmolar state	Metabolism and nutrition disorders	Electrolyte and fluid balance conditions	Electrolyte imbalance NEC	10020697
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hyperphagia	Metabolism and nutrition disorders	Appetite and general nutritional disorders	Appetite disorders	10020710
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hypertriglyceridaemia	Metabolism and nutrition disorders	Lipid metabolism disorders	Elevated triglycerides	10020869
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hypoglycaemia	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hypoglycaemic conditions NEC	10020993
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Increased appetite	Metabolism and nutrition disorders	Appetite and general nutritional disorders	Appetite disorders	10021654

Hyperglycaemia/new onset diabetes mellitus (SMQ)	Increased insulin requirement	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10021664
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Insulin autoimmune syndrome	Immune system disorders	Autoimmune disorders	Endocrine autoimmune disorders	10022472
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Insulin tolerance test abnormal	Investigations	Endocrine investigations (incl sex hormones)	Gastrointestinal, pancreatic and APUD hormone analyses	10022494
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Lactic acidosis	Metabolism and nutrition disorders	Acid-base disorders	Metabolic acidoses (excl diabetic acidoses)	10023676
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Lipids increased	Investigations	Lipid analyses	Lipoprotein and lipid tests NEC	10024592
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Loss of consciousness	Nervous system disorders	Neurological disorders NEC	Disturbances in consciousness NEC	10024855
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Metabolic acidosis	Metabolism and nutrition disorders	Acid-base disorders	Metabolic acidoses (excl diabetic acidoses)	10027417
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Obesity	Metabolism and nutrition disorders	Appetite and general nutritional disorders	General nutritional disorders NEC	10029883
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Overweight	Metabolism and nutrition disorders	Appetite and general nutritional disorders	General nutritional disorders NEC	10033307
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Polydipsia	Metabolism and nutrition disorders	Electrolyte and fluid balance conditions	Fluid intake increased	10036067
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Polyuria	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary tract signs and symptoms NEC	10036142
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Thirst	General disorders and administration site conditions	General system disorders NEC	Feelings and sensations NEC	10043458
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Unresponsive to stimuli	Nervous system disorders	Neurological disorders NEC	Neurological signs and symptoms NEC	10045555

Hyperglycaemia/new onset diabetes mellitus (SMQ)	Weight decreased	Investigations	Physical examination topics	Physical examination procedures	10047895
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Weight increased	Investigations	Physical examination topics	Physical examination procedures	10047899
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Underweight	Metabolism and nutrition disorders	Appetite and general nutritional disorders	General nutritional disorders NEC	10048828
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood glucose fluctuation	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10049803
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Impaired insulin secretion	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10052341
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hyperlipidaemia	Metabolism and nutrition disorders	Lipid metabolism disorders	Hyperlipidaemias NEC	10062060
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Central obesity	Metabolism and nutrition disorders	Appetite and general nutritional disorders	General nutritional disorders NEC	10065941

Appendix F: Background references

1. Ridker PM et al. Comparison of C-Reactive Protein and Low-Density Lipoprotein Cholesterol Levels in the Prediction of First Cardiovascular Events. *NEJM.* 2002;347:1557-1565
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW FOR
JUPITER BACKGROUND PACKAGE

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-366

Drug Name: Crestor (rosuvastatin)

Indication(s): Hypercholesterolemia

Applicant: Astra-Zeneca

Date(s): Submitted 4/8/09
User fee date 2/8/10

Review Priority: Standard

Biometrics Division: Biometrics 2 (HFD-715)

Statistical Reviewer: David Hoberman, Ph.D..

Concurring Reviewers: J. Todd Sahlroot, Ph.D.

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Background

The role of C-Reactive Protein (CRP) in the process of atherosclerosis has been examined over a number of years. Clinicians such as Dr. Paul Ridker and others have published articles estimating the association of CRP levels with the risk of major cardiovascular events (MCE) using extant databases. Several of these have shown evidence of a gradient of risk, particularly over the quintiles of CRP in large databases. In one study (AFCAPS/TexCAPS), Dr.Ridker observed that the incidence of events in the subgroup of "low LDL/ high CRP" (below/above the median with respect to each substance) 37/710 (5.2%) was similar to that in both high LDL subgroups. This finding generated the hypothesis that CRP may be an independent risk factor in a population with traditionally "low" LDL's. The JUPITER trial was designed to test whether patients without a history of coronary artery disease, with LDL < 130 mg/dL, and with CRP's greater than 2.0 mg/liter (roughly the median CRP in AFCAPS) would benefit from daily 20 mg rosuvastatin.

Design

JUPITER was an international study designed to detect a 25% reduction in risk of a major cardiac event (MCE), a composite endpoint consisting of the *first* experience of the following: fatal/non-fatal MI, fatal/non-fatal stroke, hospitalized unstable angina, or arterial vascularization. Secondary endpoints included total mortality, non-cardiovascular mortality, development of diabetes, development of deep vein thrombosis or pulmonary embolism, and bone fractures.

Subjects were randomized to placebo or 20 mg rosuvastatin. In order to achieve 90% power, the study required 514 events. Assuming an accrual period of one year and a mean follow-up of 3.5 years, the sponsor derived a sample size of 12,000, which was raised to 15,000 taking into account a possibly low placebo event rate and anticipated dropouts. A group sequential design incorporated 3 analyses with respective nominal alpha's of .003, .016, and .044. This plan corresponded to 37.5% information (195 events) at the first interim analysis, 75% information (390 events) at the second interim analysis, the final analysis at 520 events. The primary statistical analysis used the log rank test derived from the Cox proportional hazards model.

Results

After 89,846 subjects were screened 17,802 were randomized, 8901 to each treatment group. At the second interim analysis March 29, 2008, the DMC recommended termination of the study after 328 events (63% of total planned information). Approximately 7.5% of subjects in each group withdrew from the study, meaning that follow-up for MCE ceased and only vital status information was sought at the end of the trial.

The number patients randomized ranged from 14 in Uruguay to 4021 in the US, 2020 in Canada, 2873 in the UK and 2497 in South Africa.

There were 4 countries contributing at least 20 events: The US (152), Canada (66), UK (42) and South Africa (43), together accounting for 77% of the total number of MCE events. Poland, Russia, Denmark, Netherlands, Estonia, Israel, Germany, Argentina, Brazil, Mexico, Venezuela, Uruguay, Costa Rica, Guatemala, El Salvador, Panama, Colombia, Chile, Norway, Switzerland, Belgium, Bulgaria, and Romania contributed the rest.

Inclusion criteria were the following:

1. Written informed consent to participate in the study
2. Men aged 50 years and over; women aged 60 years and over (lowered from 55 years for men and 65 years for women per Amendment 4)
3. Fasting LDL-C value <130 mg/dL (3.36 mmol/L) at Screening Visit 1
4. hsCRP value ≥2.0 mg/L at Screening Visit 1
5. Triglycerides (TG) <500 mg/dL (5.6 mmol/L) at Screening Visit 1

Baseline characteristics of randomized patients were (according to the sponsor):

1) Males: 62%
2) mean age: 66
3) Whites: 71%
4) at most high school education: 59%
5) rarely/never exercise 50%, at least 2-3 times/week 38%
6) Current smokers: 16%
7) hypertension: 57%
8) family history of CHD: 11.5%
9) family history of stroke: 20.6%
10) FSG at least 100 mg/dL: 31.3%
11) Framingham Risk category: low 40.5%, Intermediate 50.5%, high 9%
12) mean BMI: 29
13) low HDL (< 40 mg/dL): 22.5%
14) metabolic syndrome: 41%

Baseline Lipid Levels mg/dL (mean of both groups)

	Mean	std
Total cholesterol	183	(24.4)
HDL-C	51	(15.3)
LDL-C	104	(18.7)
Apo A-I	165	(30.7)
Apo B	109	(21.4)
hsCRP	median 4.3 mg/L	

The following table displays the number and percentage of NCEP ATP III risk factors in each group.

	Rosuvastatin (N=8901)	Placebo (N=8901)	
1 risk factor (age only[a]), n (%)	2199 (24.7)	2080 (23.4)	4279 (24.0)
2 risk factors[b], n (%)	4373 (49.1)	4423 (49.7)	8796 (49.4)
3 risk factors[b], n (%)	1931 (21.7)	2017 (22.7)	3948 (22.2)
4 risk factors[b], n (%)	371 (4.2)	361 (4.1)	732 (4.1)
5 risk factors[b], n (%)	27 (0.3)	20 (0.2)	47 (0.3)

[a] All subjects were of increased age (inclusion criterion: men ≥50 years, women ≥60 years).

[b] Risk factors included are NCEP ATP III risk factors: age, smoking, hypertension, HDL <40 mg/dL (1.04 mmol/L), and family history of CHD

Note from the baseline table above that this subgroup comprises approximately 24% of the patients.

Primary Analysis Results

The median follow-up time to MCE or death on all randomized subjects was 2.0 years. After final adjudication of events, the sponsor reported that 2.8% (252) of the placebo subjects and 1.6% (142) of the rosuvastatin subjects had suffered a MCE. After 4 years of follow-up, the Kaplan-Meier estimates of the probability of a MCE event were 6.3% and 3.2%, respectively. The absolute treatment difference was 3.1% with a 95% confidence interval (1.7%, 4.5%). These estimates do not take into account the competing risk of non-cardiovascular deaths.

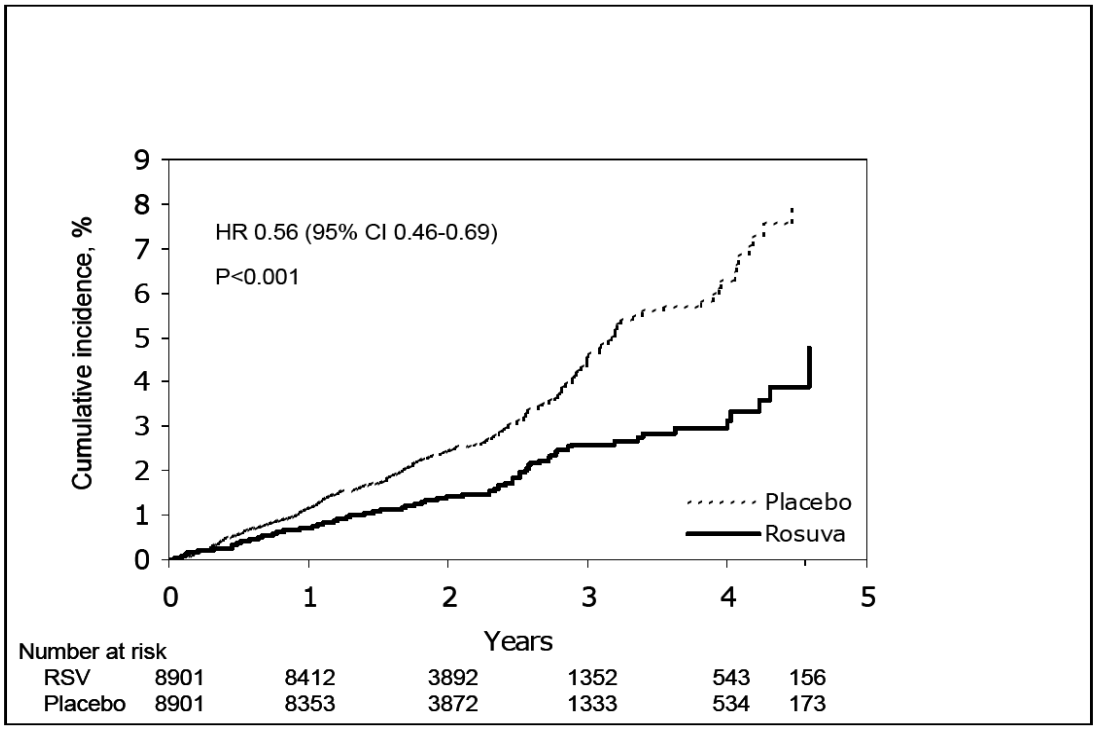
The primary analysis for time to first MCE yielded a hazard ratio of .56 with a 95% confidence interval of (.46, .69), $p<.001$. Patients were supposed to have been excluded if they had at least one cardiovascular disease "equivalent". One of these was having a Framingham 10 score greater than 20. There were 1558 subjects who met this criterion but were nevertheless enrolled in the trial. These ineligible subjects accounted for 67 events, 29 in the Rouva group and 38 in the placebo group. Deleting these 1558 subjects produces a hazard ratio of .63 with a 95% confidence interval (.42, .68). In addition, there were 1294 subjects randomized who had baseline CRP's less than 2.0. However, these accounted for only a total of 22 events.

The results for the primary analysis among the dominant four countries are displayed below:

Country	# events	hazard ratio	naïve 95% Confidence interval for hazard ratio
US	152	.63	.45-.89
Canada	66	.53	.31-.88
UK	42	.35	.17-.71
South Africa	43	.64	.34- 1.25

The figure below displays the sponsor's Kaplan-Meier plot for the primary MACE endpoint. Both the sponsor's residual analysis and log-log plots did not reveal substantial evidence of departure from proportional hazards.

Figure 4 Kaplan-Meier plot for the primary composite endpoint



Number Needed to Treat (NNT)

An alternative way to illustrate absolute treatment effect is to examine the number of subjects needed to treat in order to prevent one MCE event by different points in time. The following table displays estimates and confidence intervals for the NNT by year. They were calculated using Kaplan-Meier estimates and standard errors derived from SAS PROC LIFETEST.

		rosuva	PBO	NNT	95% CI
Survival probabilities	Year 1	.993	.988	200	(128, 460)
	Year 2	.986	.975	91	(65, 153)
	Year 3	.974	.954	50	(33, 100)
	Year 4	.968	.937	32	(22, 60)

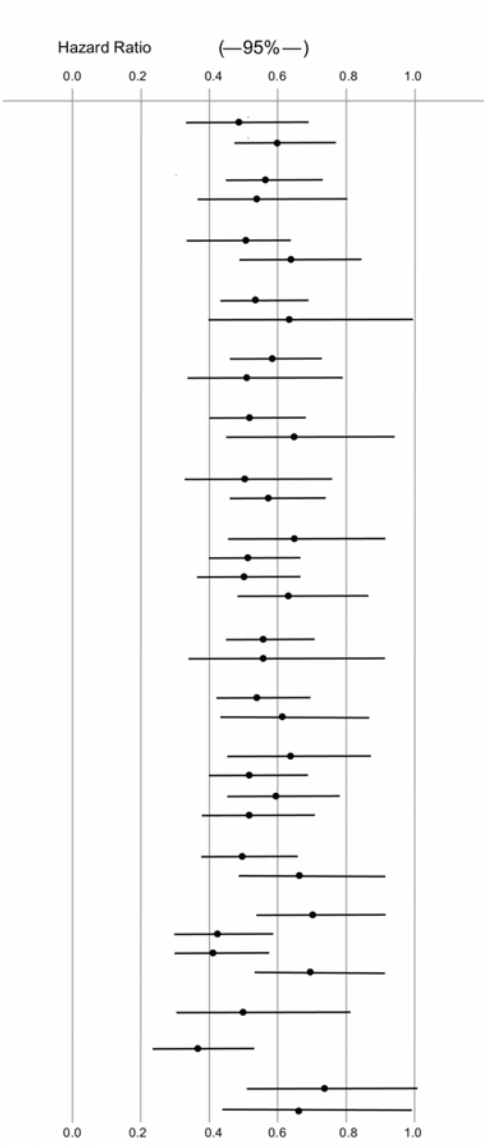
These estimates do not take into account the competing risk of non-cardiovascular deaths.

The Cox model adjusting for baseline covariates is displayed below.

Variable	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Variable Label
trt	1	0.59553	0.10580	31.6822	<.0001	1.814	TREATMENT GROUP
BMI	1	-0.04218	0.01151	13.4255	0.0002	0.959	BODY MASS INDEX (KG/M2) AT ENTRY
MS_BASE	1	0.16575	0.12225	1.8383	0.1752	1.180	METABOLIC SYNDROME AT BASELINE
B_HT	1	0.28129	0.11641	5.8386	0.0157	1.325	BASELINE HYPERTENSION GROUP
CHDRSK4	1	0.63166	0.13777	21.0212	<.0001	1.881	CIGARETTE SMOKING IN LAST MONTH
CHDRSK5	1	0.43346	0.13700	10.0104	0.0016	1.543	FAMILY HIST OF PREMATURE CHD/PVD
FRAM10	1	0.01803	0.01095	2.7118	0.0996	1.018	FRAMINGHAM 10YR RISK
AGER	1	0.05383	0.00821	43.0246	<.0001	1.055	AGE AT RANDOMIZATION (YEARS)
gen	1	-0.44117	0.15918	7.6812	0.0056	0.643	GENDER

Below is the sponsor's table of subgroup analyses.

Baseline characteristic	N of events[a] Rosuva 20 mg (N=8901) n (rate)[a]	Placebo (N=8901) n (rate)[a]	HR (95% CI)	P value for interaction
Age				
≤65 years at baseline	42 (4.9)	90 (10.3)	0.48 (0.33, 0.69)	0.338
>65 years at baseline	100 (9.9)	162 (16.6)	0.60 (0.47, 0.77)	
Sex				
Male	103 (8.8)	182 (15.5)	0.57 (0.45, 0.73)	0.817
Female	39 (5.6)	70 (10.4)	0.54 (0.37, 0.80)	
Age by sex				
Male <65 y, Female <75 y	55 (4.7)	120 (10.1)	0.46 (0.34, 0.64)	0.128
Male ≥65 y, Female ≥75 y	87 (12.9)	132 (20.1)	0.64 (0.49, 0.84)	
Race				
Caucasian	111 (7.8)	202 (14.4)	0.54 (0.43, 0.69)	0.561
Non-Caucasian	31 (7.0)	50 (11.1)	0.63 (0.40, 0.99)	
Smoker				
No	110 (6.9)	190 (12.1)	0.58 (0.46, 0.73)	0.644
Yes	32 (11.7)	62 (22.6)	0.51 (0.34, 0.79)	
Body Mass Index				
≤30 kg/m^2	94 (8.2)	179 (15.9)	0.52 (0.40, 0.67)	0.313
>30 kg/m^2	47 (6.6)	73 (10.2)	0.65 (0.45, 0.94)	
HDL-C				
< 40 mg/dL (1.0 mmol/L)	32 (7.6)	65 (15.3)	0.50 (0.33, 0.76)	0.512
≥40 mg/dL (1.0 mmol/L)	110 (7.7)	187 (13.1)	0.58 (0.46, 0.74)	
LDL-C				
≤100 mg/dL (2.6 mmol/L)	55 (8.7)	86 (13.5)	0.65 (0.46, 0.91)	0.304
>100 mg/dL (2.6 mmol/L)	87 (7.1)	166 (13.7)	0.52 (0.40, 0.67)	
Above median[b]	68 (7.0)	138 (14.1)	0.50 (0.37, 0.67)	0.236
Below median[b]	74 (8.3)	114 (13.1)	0.64 (0.48, 0.86)	
Triglycerides				
<200 mg/dL (2.2 mmol/L)	117 (7.6)	208 (13.6)	0.56 (0.45, 0.71)	0.974
≥200 mg/dL (2.2 mmol/L)	25 (7.7)	44 (13.7)	0.56 (0.34, 0.91)	
Hypertension				
Yes	89 (8.5)	166 (15.8)	0.54 (0.42, 0.70)	0.559
No	53 (6.6)	86 (10.8)	0.61 (0.43, 0.86)	
Region				
US	58 (10.7)	94 (16.9)	0.63 (0.45, 0.87)	0.395
Countries other than US	84 (6.4)	158 (12.2)	0.52 (0.40, 0.68)	
US or Canada	81 (9.7)	137 (16.3)	0.60 (0.45, 0.78)	0.536
Countries other than US/Canada	61 (6.0)	115 (11.4)	0.52 (0.38, 0.71)	
Metabolic syndrome				
No	75 (6.9)	149 (14.0)	0.50 (0.38, 0.66)	0.167
Yes	67 (8.7)	102 (13.1)	0.67 (0.49, 0.91)	
Baseline hsCRP				
above median[b]	89 (9.7)	128 (13.7)	0.71 (0.54, 0.92)	0.015
below median[b]	53 (5.6)	124 (13.5)	0.42 (0.30, 0.58)	
≤4 mg/L	50 (5.6)	119 (13.8)	0.41 (0.30, 0.57)	0.014
>4 mg/L	92 (9.5)	133 (13.5)	0.70 (0.54, 0.91)	
Baseline LDL-C and hsCRP				
below median LDL and hsCRP	24 (5.6)	47 (11.3)	0.50 (0.30, 0.81)	
above median LDL and below median hsCRP	29 (5.7)	77 (15.3)	0.37 (0.24, 0.57)	
below median LDL and above median hsCRP	50 (10.9)	67 (14.7)	0.74 (0.51, 1.07)	
above median LDL and hsCRP	39 (8.5)	61 (12.8)	0.66 (0.44, 0.99)	0.094



CI Confidence interval; HDL-C High-density lipoprotein-cholesterol; HR Hazard ratio; hsCRP high sensitivity C-reactive protein; LDL-C Low-density lipoprotein-cholesterol; Rosuva Rosuvastatin; US United States; y Years.

a Number of events and event rate/1000-person years. The denominator is the time at risk on study in days, summed across the relevant subjects and divided by 365.25. The numerator is 1000 x number of events.

b Median baseline LDL-C was 108 mg/dL (2.80 mmol/L); median hsCRP was 4.25 mg/L.

Results are consistent between various subgroups with the possible exception of below and above median hsCRP. Not shown in this table is another sponsor's table in which the only noteworthy exception to consistency in the *post-hoc* subgroups is the fact that the hazard ratio among those with less than 2 NCEP ATP III risk factors was .9. The interaction p-value for comparing the treatment effect in this subgroup vs all other

subjects was .032. This subgroup is the same as that with only the risk factor of age which is shared by all subjects in the study (See table of ATP risk factors above). The .9 hazard ratio reflects the very weak evidence of treatment benefit in this "no risk (other than age)" subgroup (33 events in the rosuvastatin group and 35 events in the placebo group).

In an article in the Journal of Thrombosis and Haemostasis [Vol 7 (suppl 1): 332-339], Dr. Ridker proposed a "age-only risk" subgroup which differs from the sponsor's in that Dr. Ridker's considered neither family history nor whether subjects were on hypertension medication. In both cases, a subject was "at risk" as hypertensive if the SBP was greater or equal to 140 or the DBP was greater or equal to 90. Thus, by including subjects who were taking hypertension medication or who had a family history of CHD in the "no risk" subgroup, Dr. Ridker's subgroup contains 6375 patients, whereas the sponsor's contains 4279. Dr. Ridker's subgroup produced a hazard ratio of .63 with 95% CI (0.44-0.92) with 45 events in the rosuvastatin group and 72 in the placebo group. Thus we find that Dr. Ridker's subgroup adds 37 MCE events to the placebo group and 12 MCE events to the rosuvastatin group, largely contributed by subjects who were taking hypertension medication.

MCE Components

The table below displays the number of *first* MCE events for each component.

First MCE	rouvastatsin	Placebo
Total	142	252
Cardiovascular death	29	37
Nonfatal MI	21	61
Non Fatal Stroke	30	57
Hospitalized Unstable Angina	15	27
Arterial revascularization	47	70

If a subject had more than 1 MCE on the same day, only 1 event is shown according to the following hierarchy: 1) instable angina, 2) MI, 3) arterial revascularization, 4) non-fatal stroke, 5) cardiovascular death.

The incidence rates were 7.6 and 13.6 per 1000 patient years in the rosuvastatin and Placebo groups, respectively.

The sponsor's table below displays the statistical results for each component **including MCE events subsequent to the first**. Thus a subject can occur in more than one row. It does not count repeated events of the same kind.

	rosuvastatin	placebo

	n %	n %	HR(95% CI)	p-value
Cardiovascular death	35 (0.4)	44 (0.5)	0.80 (0.51, 1.24)	0.315
Nonfatal stroke	30 (0.3)	58 (0.7)	0.52 (0.33, 0.80)	0.003
Nonfatal MI	22 (0.2)	62 (0.7)	0.35 (0.22, 0.58)	<0.001
Hospitalized unstable angina	16 (0.2)	27 (0.3)	0.59 (0.32, 1.10)	0.093
Arterial revascularization	71 (0.8)	131 (1.5)	0.54 (0.41, 0.72)	<0.001

Non-fatal Stroke, non-fatal MI, and arterial revascularization are statistically significant.

Lipid Lowering

Approximately 90% of subjects were available for lipid measurements at one year. After that point, data was scarce. The table below displays the sponsor's figures for **the mean percent change from baseline at one year** in each group:

	rosuvastatin	placebo	p-value
Total Cholesterol	-23.6%	-3.3%	< .001
HDL-C	7.6%	3.0%	<.001
LDL-C	-45.3%	5.4%	<.001
TG	-9.4%	6.8%	<.001
hsCRP	-12.9%	15.7%	<.001
hsCRP **median** change	-46.9%	-20.2%	

Secondary Endpoints

The results of the specified secondary endpoints subject to a sequential testing procedure are listed in the table below.

	rosuvastatin		placebo			
	n	%	n	%	HR(95% CI)	p-value
CV death/MI/stroke	83	(0.9)	158	(1.8)	0.52 (0.40, 0.68)	<0.001
Fatal or nonfatal MI	31	(0.3)	68	(0.8)	0.46 (0.30, 0.70)	<0.001
Fatal or nonfatal stroke	33	(0.4)	64	(0.7)	0.52 (0.34, 0.79)	0.002

Although Total Mortality (p=.021, HR=.80) was statistically significant at the .05 level when vital status data was used, it was neither a component of the MCE endpoint nor a secondary endpoint subject to Type I error control in the Statistical Analysis plan (SAP).

There were 198 deaths (2.2%) in the rosuvastatin arm and 247 deaths (2.8%) in the placebo arm. The Kaplan-Meier estimates at 4 years were 4.2% and 5.3% respectively, with an absolute risk difference of 1.1% and 95% confidence interval (0.3%, 1.9%).

Further inspection of the data shows that the Kaplan-Meier curves converge toward the end of the trial. At approximately 1600 days (4.4 years), the Kaplan-Meier estimate of the absolute difference in risk of death is 0.7% in favor of rouvastain with a 95% confidence interval (-0.4%, 1.8%). Thus, it is not clear whether or not rosuvastatin confers a total mortality advantage compared to placebo even though the logrank test appears to detect the separation of the survival curves up to over 4 years.

APPENDIX

The Log-Hazard as a Biased Estimator in the Planned Trial

When trials stop early at an interim analysis, the estimator used to measure treatment effect can be biased away from the 'true population' value. This section provides an asymptotic method for estimating the maximum bias using the estimated β-coefficient (βhat) derived from the Cox model with the treatment indicator as the only term. For simplicity, we regard the chances of stopping at the first look (190 events) as remote, so we deal only with stopping at the second look (390 events) or continuing to the end (520 events). In addition, we apply results that obtain using the central limit theorem with known variance to the asymptotic case of the log rank analysis as it applies to the Cox proportional hazards model with only the treatment 0-1 variable in the model. This is possible because standard results calculate the standard error of the log hazard ratio to be close to 2/sqrt(D), where D is the number of events at an interim analysis. Since this number has been fixed before the trial, we do not need to regard the standard error as a random variable.

The bias is calculated as the difference between two weighted conditional expectations. The first expectation is E(βhat| βhat exceeds the its critical value (z=2.41 on the normalized scale) at the second look. The weight is the power or probability it will do so under alternatives to the null, in this case the null being β=0. The second expectation is E(βhat| βhat *does not* exceed the its critical value at the second look), i.e. the trial goes to completion. Its weight is 1-power. For the log hazard ratio, the difference between these two terms gives the bias *on the log scale.* Since 1) the plan anticipated 75% of the total information by the second analysis and 2) the fact that the standard error of the log hazard estimate at the second look would be .10, while that at the planned end of the trial would be very similar (.088), we expect any bias to be very modest. In fact, the maximum biased estimate of the hazard ratio itself is only 1% away from the 'true value' of the hazard ratio in the realistic range of 1.0 to 2.0.